The New England
Journal of Medicine

Copyright, 1946, by the Massachusetts Medical Society

Volume 234 APRIL 4, 1946 Number 14

THE PENETRATION OF PENICILLIN THROUGH NORMAL AND INFLAMED MENINGES*

LIEUTENANT COLONEL J. MURRAY KINSMAN, M.C., A.U.S., AND
CAPTAIN C. ANTHONY D'ALONZO, M.C., A.U.S.

FOLLOWING the demonstration that penicillin exhibits a remarkable antibacterial effect against organisms frequently causing meningitis, there immediately arose the question of the most effective mode of its administration in patients with these infections. Before penicillin was used in the treatment of meningitis, it was necessary to study its distribution in the body, particularly in the spinal fluid after extrathecal administration. Rammelkamp and Keefer[1] demonstrated that the meninges and the choroid plexus form a partial barrier against the passage of the drug from the blood stream into the spinal fluid, both in normal persons and in patients with meningitis. As a result of their investigations, it became the practice to give penicillin both extrathecally and intrathecally when it was used in purulent meningitis.

In general, the results with this combined form of therapy have been good.[2, 3] Recently, however, McDermott, Eagle and Nelson[4] have shown that low concentrations — those of 0.02 units per cubic centimeter or less — of penicillin appear in the spinal fluid of normal persons several hours after massive parenteral doses. That inflamed meninges are more susceptible to the passage of penicillin than are normal ones was suggested by experiments in which constant amounts of the drug were injected intrathecally and assays of the blood and spinal fluid were performed at intervals thereafter. These studies showed that when the meninges are inflamed, the penicillin is absorbed from the spinal fluid more rapidly than it is in normal subjects.[5] Evidence tending to confirm these observations has been presented by Fleming[6] and more recently by Rosenberg and Sylvester.[7] The latter reported that they had found penicillin in the spinal fluid in patients with meningitis who had been treated by the intramuscular or the intravenous route alone. Price and Hodges[8] reported that 4 patients were cured, both clinically and bacteriologically, following extrathecal therapy; 3 of them had meningococcal meningitis and 1 had pneumococcal meningitis. They mention 2 other patients in whom the cause of recovery was difficult to evaluate because they had received large doses of sulfonamides prior to penicillin therapy. In none of these cases were assays of the blood or spinal fluid performed. These observations have naturally suggested that intrathecal administration of penicillin is not necessary.

On the other hand, there is evidence that extrathecal therapy alone is sometimes inadequate. Some patients with pneumococcal pneumonia have developed pneumococcal meningitis while under treatment with penicillin administered by the intramuscular route.[9] Moreover, in a few patients with pneumococcal[9] and meningococcal[10] meningitis there was a poor response to penicillin therapy until it was given intrathecally.

Because of the conflicting reports, it seemed advisable to obtain further information concerning the most efficient mode of administration of penicillin in patients with meningitis; this was considered especially important because of the comparatively high incidence of meningitis in wartime. Studies have been conducted in this hospital concerning the penetration of penicillin into and out of the spinal fluid. The results of these studies, together with certain clinical observations concerning the effectiveness of extrathecally administered penicillin in the treatment of meningococcal meningitis, comprise the present report.

ASSAY OF SPINAL FLUID FOLLOWING INTRATHECAL ADMINISTRATION

To determine how long penicillin persists in the spinal fluid after intrathecal administration, 4 patients with meningococcal meningitis were treated according to the following schedule: a dose of 25,000 units was given intravenously and one of 10,000 units intrathecally at the same time; one hour later, a dose of 25,000 units was given intramuscularly and repeated every three hours; the intrathecal injection was again administered at the

*From the Medical Service, Regional Station Hospital, Fort Bragg, North Carolina.
Part of this study was done under the direction of Lieutenant Colonel Worth C. Daniels, M.C., A.U.S.

eighth hour. Spinal fluid was collected for assay at the eighth and twenty-fourth hours. The specimens taken at the eighth hour contained 3.9 to 20.0 units per cubic centimeter, and those taken at the twenty-fourth hour contained 0.078 to 0.312 units. The penicillin content of the spinal fluid eight hours after the intrathecal injection of 10,000 units was thus shown to be far in excess of the minimum therapeutic requirement, and sixteen hours later, after a second intrathecal injection of 10,000 units, it was still at a therapeutically effective level. This indicates that when penicillin is used intrathecally for meningitis, it is not necessary to repeat the injections oftener than once every sixteen hours. Moreover, further observations in the same cases suggest that injection once every twenty-four hours is sufficient.

Assays of Spinal Fluid Following Extrathecal Administration

In Patients Without Meningitis

More than 20 patients with early syphilis without meningitis were given intramuscular injections of 20,000 to 40,000 units of penicillin every three hours for one to eight days, and the spinal fluid was assayed at various intervals from the fifth to the eighth day. In no case was penicillin detected in the spinal fluid.

In Patients with Meningococcemia

Since it is now generally accepted that meningococcal meningitis is a sequel to or a metastatic form of a bacteremic phase, it was thought that in meningococcemia penicillin might possibly diffuse more readily into the spinal fluid than it does in normal persons. Specimens of the spinal fluid of 6 patients with meningococcemia who were being treated by penicillin were therefore collected for assay. Five of the patients received an initial dose of 25,000 units intravenously, which was repeated one hour later and then every three hours day and night. The spinal fluid was collected at the eighth and twenty-fourth hours of treatment in 4 cases and at the fifth and ninth days in 1 case. The sixth patient was on the same schedule, but in this case each dose was 40,000 units and the spinal fluid was collected at the eighth and twenty-fourth hours. In not one of the twelve specimens of spinal fluid was any penicillin detected, although in every case the clinical response to treatment was excellent and in no case did meningitis develop.

In Patients with Meningitis

Tuberculous meningitis. Prior to making observations on patients with meningococcal meningitis, 2 patients with tuberculous meningitis were given penicillin by extrathecal injections and spinal fluid was obtained for assay. One patient was given five doses of 40,000 units each over a period of ten hours; the specimen of spinal fluid taken at the eleventh hour contained a trace of penicillin, whereas that taken at the twenty-ninth hour contained none. The other patient received 40,000 units every three hours for eight doses; at the eighteenth hour no penicillin could be found in either the blood or the spinal fluid, whereas at the twenty-third hour the blood contained 0.4 units per cubic centimeter and the spinal fluid a trace of penicillin. In spite of large doses, therefore, only a trace of penicillin could be found in the spinal fluid after eleven hours of treatment in one case and after twenty-three hours of treatment in the other.

Meningococcal meningitis. In view of the reported successes in treating meningococcal meningitis with penicillin administered only extrathecally, a study was made of the distribution of penicillin and its effectiveness in this disease when administered by the intramuscular route. Two case reports illustrating these points follow.

Case 1. A 33-year-old soldier was admitted to the hospital on November 18, 1944, at 3:40 p.m. At 8 a.m. of that day he had had a chill, and he later developed a splitting headache. On admission he showed fever, an erythematous rash, marked rigidity of the neck, bilateral Kernig and Brudzinski signs, absent knee jerks and drowsiness. The spinal fluid contained 1540 cells per cubic millimeter, gram-negative intracellular diplococci were found on the smear, and Group I meningococcus was obtained from the culture.

It was decided to treat the patient with penicillin by the extrathecal route alone. Accordingly, at 5:45 p.m. he was given 40,000 units intravenously (Fig. 1). One hour later

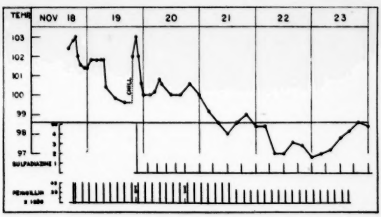

Figure 1. *Case 1.*

This is the temperature curve of a patient with meningococcal meningitis who was treated initially only with penicillin. The dotted lines under 1 in the penicillin dosage zone represent intrathecal injections.

he received 40,000 units intramuscularly, and this dose was repeated every 3 hours. During the next 24 hours the temperature fell to 99.6°F., the rash disappeared, the Kernig sign became less pronounced, the knee jerks returned, and the patient became less lethargic and drowsy. The headache, however, appeared to be as severe as ever. The spinal-fluid cell count rose to 9000 by 8:45 a.m. on November 19 and dropped to 3450 at 5:45 p.m., and the pressure fell from 210 to 125 mm. (Table 1). All specimens subsequently yielded meningococci on culture. At 7:20 p.m. on November 19, 25 hours after the first dose of penicillin, the patient had a sudden chill, and the temperature rose to 102° F. and a half-hour later to 103° F. At the same time the headache became still severer, the rigidity of the neck increased, the Kernig sign became more pronounced, and the patient became more lethargic. The spinal fluid obtained 1 hour after the chill contained 6200 cells, almost twice as many as did the speci-

men taken 3 hours previously, and the pressure had risen from 125 to 285 mm. At 9 p.m. sulfadiazine therapy was instituted in addition to the penicillin, which was continued, and from this time on the patient made a rapid and complete recovery. Blood cultures taken throughout the course of the illness were negative.

Comment. For a while this patient appeared to be responding to penicillin, although the improvement was less rapid than that usually produced by sulfadiazine. Taking into consideration the clinical relapse and the supporting bacteriologic evidence, however, the case must be definitely classified as one of failure of penicillin to effect a cure. It is of interest that the only time a measurable level of penicillin was present in the spinal fluid was 27 hours after parenteral therapy was instituted, shortly before sulfadiazine was administered (see Table 2).

CASE 2. An 18-year-old soldier was admitted on January 20, 1945. He apparently had a mild upper respiratory infection, and was about to be discharged on January 22 when he had a chill, followed by fever. He gradually developed a splitting headache, a sore throat and stiffness of the neck. Examination later in the day showed a fine macular eruption, moderate rigidity of the neck, positive Kernig and Brudzinski signs and sluggish reflexes. By this time the patient was semicomatose. A diagnosis of meningococcal meningitis was established by examination of the spinal fluid, which contained 4650 cells per cubic millimeter and in which gram-negative intracellular organisms were demonstrated on smear (Table 3).

Because it was possible to keep the patient under close observation, it was decided to begin therapy with penicillin alone. This was begun at 10 p.m. on January 22 with a dose of 40,000 units intravenously and 40,000 units intramuscularly, the latter being repeated at 11 p.m., midnight and 1 a.m. and every 3 hours thereafter. There was some clinical improvement (Fig. 2) but not of a marked degree, and because the patient's condition remained poor, sulfadiazine therapy was begun on January 23, 20 hours after the first dose of penicillin. A little later the temperature rose to 103°F. Both sulfadiazine and penicillin were continued, and there was rapid and complete recovery. Blood cultures taken throughout the course were negative.

Comment. As in Case 1, there was an initial improvement followed by a relapse and sulfadiazine was necessary for cure. In this case the relapse occurred 20 hours after the institution of penicillin therapy, as compared with 25 hours in Case 1. No penicillin was found in the spinal fluid at any time (see Table 2). Throughout the period of penicillin therapy the cell count remained elevated and both smears and cultures were positive.

TABLE 1. *Spinal-Fluid Findings in a Case of Meningococcal Meningitis (Case 1).*

DATE	HOUR	PRESSURE	APPEARANCE	NO. OF CELLS	POLYMORPHONUCLEAR CELLS	SMEAR	CULTURE
		mm.			*%*		
11/18/44	5:20 p.m.	—	Cloudy	1,540	95	Meningococcus	Meningococcus, Group I
11/19/44	1:45 a.m.	210	Cloudy	6,250	96	Negative	Negative
	8:45 a.m.	140	Cloudy	9,000	93	Negative	Meningococcus, Group I
	5:45 p.m.	125	Cloudy	3,450	88	Negative	Meningococcus, Group I
	8:45 p.m.	285	Cloudy	6,200	88	Negative	Negative
11/20/44	5:45 p.m.	110	Cloudy	4,350	87	Negative	Negative
11/23/44	10:00 a.m.	68	Clear	6	50	Negative	Negative

TABLE 2. *Assays of Blood and Spinal Fluid for Penicillin in 8 Patients with Meningococcal Meningitis Who Received Penicillin Extrathecally.*

CASE NO.	DOSAGE OF PENICILLIN	INTERVAL BETWEEN INJECTION AND COLLECTION	PENICILLIN CONTENT	
			BLOOD	SPINAL FLUID
		hr.	*units/cc.*	*units/cc.*
1	40,000 units intravenously; 40,000 intramuscularly 1 hr. later and every 3 hr. thereafter.	8	0.3125	0
		15	0	0
		24	0.3125	0
		27	0.0195	0.04
2	40,000 units intravenously and 40,000 units intramuscularly; 40,000 units intramuscularly 1, 2 and 3 hr. later and every 3 hr. thereafter.	1½	1.0	0
		2½	0.5	0
		10	0	0
		16	0	0
3	Same as in Case 2	1½	1.0	0.05
		2½	1.0	0.04
4	Same as in Case 2	1½	0.5	0
		2½	0.5	0.05
5	Same as in Case 2	1½	0.4	0
		2½	0.5	0
6	Same as in Case 2	2½	—	0.05
7	25,000 units intramuscularly, repeated 1 hr. later; 40,000 units intramuscularly 3 hr. later and every 3 hr. thereafter.	22	—	0.05
8	40,000 units intramuscularly; 100,000 units intravenously 1 hr. later; 25,000 units intramuscularly 5 hr. later and every 3 hr. thereafter.	35*	—	0*
9	30,000 units intravenously; 100,000 units intravenously ½ hr. later; 20,000 units intramuscularly 3 hr. later.	5†	—	Trace†

*Patient died at 35th hour after the first injection; spinal fluid was collected at autopsy 13 hours later.
†Patient died at 5th hour after the first injection; spinal fluid was collected at autopsy 2 hours later.

Following these experiences there was felt a natural reluctance to attempt to treat other patients with penicillin by the extrathecal route alone. Since, however, Rosenberg and Sylvester[7] had found penicillin in the spinal fluid in 8 patients at one and a half and two and a half hours after a single intramuscular injection of 40,000 units of penicillin, it was decided to attempt to confirm

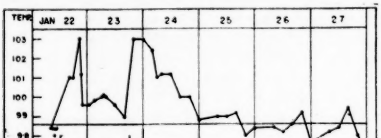

FIGURE 2. *Case 2.*

This is another temperature curve of a patient with meningococcal meningitis who was treated initially only with penicillin.

their results without jeopardizing the life of the patient by withholding other treatment. To be certain that a high concentration of penicillin was present in the blood stream, the doses used were large: at the outset a 40,000-unit dose was injected intravenously and the same dose intramuscularly. This dose was again given intramuscularly and 2 hours later. Specimens of blood and spinal fluid were collected for assay one and a half and two and a half hours after the beginning of treatment, after which the patients were placed on sulfadiazine. The results in 4 cases (Cases 3, 4, 5 and 6) are recorded in Table 2, which also incorporates the results in the 2 cases reported above and in 3 cases (Cases 7, 8 and 9) in which assays were done at odd intervals. These studies showed that penicillin may indeed penetrate into the spinal fluid, although it does so irregularly and in low concentrations. Concentrations of the order reported by Rosenberg and Sylvester — that is, up to 0.35 units per cubic centimeter) — were not found in a single case, the highest level being 0.05 units. It should be emphasized that the blood levels were usually high — either 0.5 or 1.0 units per cubic centimeter — when measured at one and a half and two and a half hours after the beginning of treatment in 3 cases (Cases 3, 4 and 5) of the 4 in which extremely large doses were given in the beginning.

TABLE 3. *Spinal-Fluid Findings in a Case of Meningococcal Meningitis (Case 2).*

DATE	HOUR	APPEARANCE	NO. OF CELLS	POLYMORPHONUCLEAR CELLS %	SMEAR	CULTURE
1/22/45	9:00 p.m.	Turbid	4,650	96	Meningococcus	Meningococcus, Group I
	11:30 p.m.	Cloudy	8,300	93	Meningococcus	Meningococcus
1/23/45	12:30 a.m.	Cloudy	10,500	91	Meningococcus	Meningococcus
	8:00 a.m.	Cloudy	7,200	90	Meningococcus	Meningococcus
	2:00 p.m.	Cloudy	9,500	90	Meningococcus	Meningococcus

DISCUSSION

The studies reported herein indicate that although parenterally administered penicillin may penetrate into the spinal fluid in patients with meningitis, it does so irregularly and in relatively low concentrations. These observations do not confirm those of Rosenberg and Sylvester,[7] who found measurable spinal-fluid levels in all of 10 cases of meningitis, with some values as high as 0.35 units per cubic centimeter. The differences are undoubtedly due in part to the fact that the assays in the present study were done by a modification of the Rammelkamp[11] serial dilution test, whereas Rosenberg and Sylvester used a turbidimetric method. A detailed discussion of assay procedures is beyond the scope of this paper, but in general it may be said that owing to the variable factor of lysis of sensitive staphylococci by penicillin, the reliability of turbidimetric methods such as that employed by Rosenberg and Sylvester is open to serious question. The fact that certain of the values that they obtained — as high as 0.35 units per cc. — are so much higher than those in the present study following much larger doses of penicillin and than those obtained in other laboratories[4] makes this explanation all the more probable.

The fact that the 2 patients in the present series who failed to respond to extrathecal therapy alone did not have measurable amounts of penicillin in the spinal fluid, except for a trace on one occasion, presumably indicates an inability of the penicillin to penetrate readily into and through the meninges. This does not invalidate the favorable results obtained by Price and Hodges[8] from administration by the extrathecal route alone, but merely emphasizes the variability and irregularity in the appearance of therapeutic concentrations of penicillin in the spinal fluid when the drug is given in this manner.

The recent studies of Meads and his associates[12] reveal important information concerning a subject closely related to the problem of parenteral versus intrathecal therapy. It was found that certain strains of meningococci were relatively resistant to penicillin, some of them so much so that even with intrathecal and extrathecal penicillin therapy combined the results were not so good as those obtained

with sulfadiazine. These observations indicate that if penicillin is to be used in the treatment of meningitis, the concentration in the meninges and spinal fluid should be high enough to be effective against the relatively resistant organisms occasionally encountered. From the present studies, it is evident that when given only extrathecally penicillin penetrates into the spinal fluid too irregularly and in concentrations too small to satisfy fully these requirements. An exception to this is syphilitic meningitis, in which penicillin administered intramuscularly appears to give excellent results.[13, 14]

Four main points indicating that extrathecal therapy alone is not effective in meningitis have emerged from the present studies and from previous reports. These are the development of pneumococcal meningitis in patients receiving extrathecal penicillin therapy for pneumococcal pneumonia; the failure of many patients with pneumococcal and meningococcal meningitis to respond to penicillin until it was administered intrathecally; the low concentrations and irregularity of appearance of penicillin in the spinal fluid of patients with meningitis following extrathecal administration alone; and the fact that many cases of meningitis are caused by meningococci that are relatively resistant to penicillin.

It is therefore our opinion that patients with pneumococcal, streptococcal or staphylococcal meningitis should receive penicillin by both the extrathecal and intrathecal routes. For meningococcal meningitis, sulfadiazine is probably preferable to penicillin, but here too, if penicillin is administered, it should be given both extrathecally and intrathecally.

Summary and Conclusions

Because of the conflicting evidence for and against the intrathecal versus the extrathecal administration of penicillin in the treatment of meningococcal meningitis, a study has been made concerning the penetration of this drug into and through the spinal fluid.

When doses of 10,000 units of penicillin were injected intrathecally in patients with meningococcal meningitis who were also receiving moderately large doses intramuscularly, therapeutically effective amounts were still present in the spinal fluid sixteen hours later.

In more than 20 patients without meningeal involvement who were given intramuscular injections of 10,000 to 25,000 units of penicillin every three hours, penicillin was not found in the spinal fluid in a single case after five to eight days of therapy.

In 5 patients with meningococcemia without meningitis who received 25,000 units of penicillin intramuscularly every three hours, and in 1 who was given 40,000 units on the same schedule, penicillin was not found in the spinal fluid in any case after eight and twenty-four hours of therapy in 5 cases and after five and nine days in 1 case. Every patient recovered, and in no case did meningitis develop.

In 2 patients with tuberculous meningitis who were treated extrathecally alone, only a trace of penicillin could be found in the spinal fluid — after eleven hours of treatment in one case and after twenty-three hours of treatment in the other.

In 9 patients with meningococcal meningitis who were treated during the early part of their illness with penicillin extrathecally only, assays of the spinal fluid were performed at various time intervals after the beginning of therapy. In some cases no penicillin could be demonstrated in the spinal fluid at any time up to thirty-five hours; in others small amounts, never larger than 0.05 units per cubic centimeter, were found. The appearance of penicillin in the spinal fluid after large extrathecal doses was irregular and inconstant.

The case histories of 2 patients with meningococcal meningitis who were treated with comparatively large doses of penicillin extrathecally are presented. In each case relapse occurred after an initial period of improvement — after twenty hours of therapy in one case and after twenty-five hours of therapy in the other. Both patients promptly recovered under sulfadiazine therapy.

Penicillin penetrates the meningeal barrier too erratically to justify its use extrathecally alone in purulent meningitis.

References

1. Rammelkamp, C. H., and Keefer, C. S. Absorption, excretion and distribution of penicillin. *J. Clin. Investigation* **22**:425-437, 1943.
2. Rosenberg, D. H., and Arling, P. A. Treatment of cerebrospinal fever with penicillin. *U. S. Nav. M. Bull.* **43**:281-287, 1944.
3. Cairns, H., Duthie, E. S., Lewin, W. S., and Smith, H. V. Pneumococcal meningitis treated with penicillin. *Lancet* **1**:655-659, 1944.
4. McDermott, W., Eagle, H., and Nelson, R. A. Unpublished data.
5. Rammelkamp, C. H., and Keefer, C. S. Absorption, excretion and toxicity of penicillin administered by intrathecal injection. *Am. J. M. Sc.* **205**:342-350, 1943.
6. Fleming, A. Streptococcal meningitis treated with penicillin: measurement of bacteriostatic power of blood and cerebrospinal fluid. *Lancet* **2**:434-438, 1943.
7. Rosenberg, D. H., and Sylvester, J. C. Excretion of penicillin in spinal fluid in meningitis. *Science* **100**:132, 1944.
8. Price, A. H., and Hodges, J. H. Treatment of meningitis with penicillin injected intravenously and intramuscularly. *New York State J. Med.* **44**:2012-2014, 1944.
9. Anderson, D. G. Treatment of infections with penicillin. *New Eng. J. Med.* **232**:400-405, 1945.
10. Dawson, M. H., and Hobby, G. L. Clinical use of penicillin: observations in 100 cases. *J. A. M. A.* **124**:611-622, 1944.
11. Kirby, W. M. M., and Rantz, L. A. Methods of measuring penicillin concentrations in body fluids. *J. Bact.* **48**:603-608, 1944.
12. Meads, M., Harris, H. W., Samper, B. A., and Finland, M. Treatment of meningococcal meningitis with penicillin. *New Eng. J. Med.* **231**:509-517, 1944.
13. Nelson, R. A., and Duncan, L. Acute syphilitic meningitis treated with penicillin. *Am. J. Syph. Gonorr. & Ven. Dis.* **29**:141-164, 1945.
14. Gammon, G. D., Stokes, J. H., Beerman, H., Ingraham, N. R., Lentz, J. W., Morgan, H. G., Steele, W., and Rose, E. K. Penicillin in neurosyphilis: effect on blood and spinal fluid. *J. A. M. A.* **128**:653, 1945.

CLOSURE OF COLOSTOMIES
With Report of a Case

LIEUTENANT COLONEL PHILIP S. FOISIE, M.C., A.U.S.*

THE abdominal cavity, on account of its size and central location, offers a conspicuous target for pieces of flying shell fragments, so that it is not surprising that every trainload of recently wounded patients arriving at an Army general hospital includes a fair number with abdominal injuries. Those that we have received were in fair condition on admission. In a few cases, the wound had been closed when exploration revealed no perforation of the bowel. In some, large hematomas had been found or other nonintestinal injuries had been repaired, but in the largest group of cases there was a history of bowel perforation, often multiple. In most of these, wounds of the small bowel had been sutured or resections had been done when the trauma was extensive. Many of these patients had primary closure with good results. In most cases of injury to the large bowel, the injured site had been exteriorized; and most cases that presented any great amount of bowel damage had received colostomy. Only in occasional cases did the record state that the limbs of bowel had been sutured together to form a well defined spur. By digital examination, however, it was possible to decide which cases were suitable for crushing, and most of the cases were prepared for closure in this manner. In 26 cases, colostomies were closed by applying clamps to reduce the septum between the bowel loops, and this was followed by simple transverse suture of the stoma, after the bowel had been freed to below the peritoneum and the adjacent rim of skin, with any protruding and edematous portion of the bowel, had been resected. It was usually found that this section of the bowel was fairly well walled off from the general peritoneal cavity by intraperitoneal adhesions, and no attempt was made to free them. After closure the bowel was dropped into the abdominal cavity and the peritoneum was closed over it, but the adhesions were not completely freed in the general peritoneal cavity. These patients had extremely little postoperative reaction or distention. Such a procedure can be carried out through a small elliptical incision, a small margin of skin around the stoma being excised, even when it is situated well in the flank or close to the inguinal region.

In only 2 cases were the loops resected and the free ends anastomosed. In one of these, a large mass of bowel had been exteriorized onto the abdominal wall following extensive injury to the descending colon. In the other case, a large amount of protruding bowel was eroded and thickened from exposure and was so situated laterally as to offer little opportunity for freeing it up in situ. In this case the bowel was closed externally, covered with a rubber glove and brought back into the abdomen, and after resection of the entire mass a lateral anastomosis done.

Whether the limbs of bowel are sutured together to form a spur suitable for subsequent crushing or a loop of bowel is brought to the surface with no attempt to approximate its limbs, a certain amount of spur is bound to result. Efferent and afferent limbs adhere to some extent by their approximation in passing through the abdominal wall. All that is necessary to allow room enough for subsequent closure is to crush a portion of the intervening septum. Almost any type of surgical forceps is satisfactory for this purpose. The Kelly forceps suffices when only a small bite needs to be taken, but it is rarely comfortable to close the instrument to the first notch when it is first applied, and since it has no tooth at the tip, it is likely to slip off as the edema subsides. The Ochsner forceps overcomes this disadvantage but takes an extremely small bite. We generally use a pylorus clamp for the first application, employing the Kelly forceps later if a little more of the septum must be taken. The instrument is closed only to the point where it begins to be uncomfortable, and the bite is held with a strip of adhesive tape around the handles of the forceps. The slack can be taken up gradually every two or three hours with new strips as edema subsides until the first notch is reached. It is not necessary to apply two parallel clamps and slough out the central section. As soon as a cut is made in the septum it separates, and this forms an adequate lumen.

A practical criterion as to the adequacy of the preparation is the patient's ability to resume normal bowel movements. Patients admitted with evacuation occurring exclusively through the abdominal stoma begin to have normal defecations after some of the opposed bowel wall has been crushed. We have frequently tested this function by plugging the stoma with a vaseline gauze pack supported by a firm pressure dressing. This serves to encourage normal defecation if the lumen is adequate and also reduces any herniation of the bowel, as well as any edema in the exposed portion. Occasionally this results in complete reduction of the bowel beneath the skin margin and almost complete spontaneous closure. We have not waited for this to occur, however, since it still leaves bowel tied into the abdominal wall and requires unnecessary time. In such cases it is necessary only to excise the skin margin and close the small remaining opening into the bowel with a purse-string suture.

*Instructor in surgery, Tufts College Medical School and assistant to visiting surgeons, Boston City Hospital (on leave of absence).

The bowel can then be freed from the abdominal wall, the peritoneum closed over it, and the defect in the abdominal wall repaired. The wound is closed without drainage.

In some circumstances there is some question whether sufficient lumen has been left after closure of the bowel. This happens when the opening is particularly large so that its inversion with two layers of sutures may have encroached too much on the amount of lumen present. This is particularly true when the absence of a well defined spur has made it advisable to do little or no crushing. In such cases a transverse closure is done, and if it is thought that this has resulted in a questionably small lumen at the point of closure, an auxiliary stoma is made by a lateral anastomosis of the adjacent limbs as they lie side by side in the portion of the bowel that traverses the abdominal wall

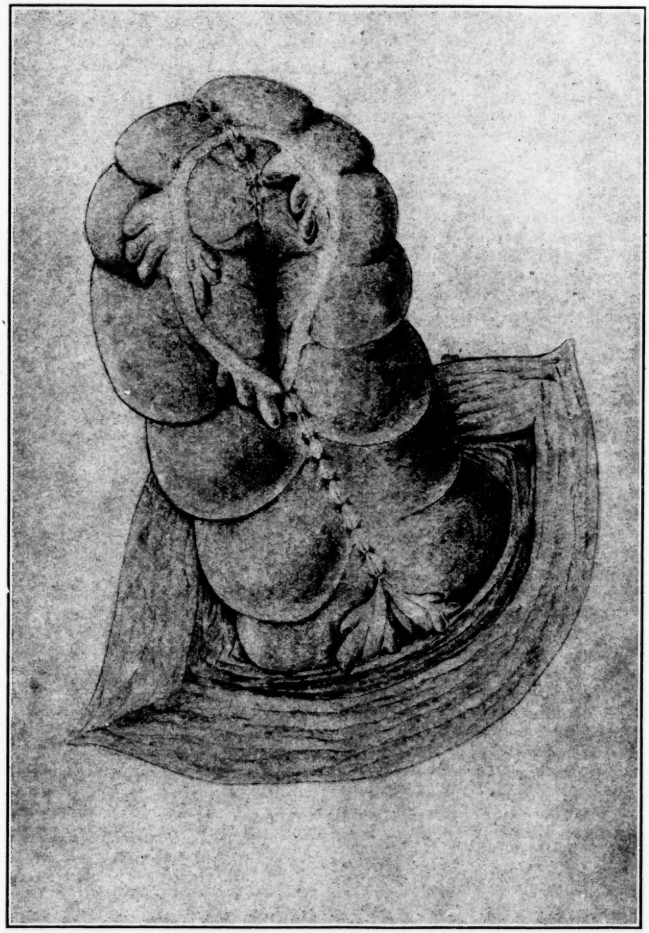

FIGURE 1. *Completed Closure by Transverse Suture at the Site of Colostomy, with Anastomosis of Adjacent Loops in Cases in Which the Closure Leaves a Lumen of Questionable Adequacy.*

(Fig. 1). This is done through the smooth longitudinal band of the antimesenteric margin, which can be easily approximated, since these loops of bowel are usually found bound together by adhesions incident to their displacement into the abdominal wall. In this way a satisfactory intestinal stream is re-established without sacrificing any blood supply to the bowel and without breaking through the protective walling-off process that to some extent at least seals off the local area of affected bowel from the general peritoneal cavity. Apart from the safety factor that this more conservative procedure affords, the postoperative course is milder than it is in cases in which resection and anastomosis are done.

Preoperative Preparation

As soon as colostomy patients are admitted, the record is studied to learn the extent and nature of the original bowel injury and to ascertain what was done at the forward hospital. A digital examination of the stoma is then made to determine whether the loops lie in close approximation and to gauge the thickness of the intervening septum. If the loops diverge immediately and there is a bulk of intervening tissue, no crushing is attempted. In most cases the two loops are found to lie parallel for several centimeters, with only a thin septum consisting of the two bowel walls, so that there is ample opportunity for crushing between them, even when the record makes no mention of the formation of a well defined spur. Clamps are applied as described above, several small bites being taken in preference to including too much tissue in the first application. The clamps usually fall off in three days, and a day or two more is allowed for any edema to subside before making a reapplication, if this is considered necessary. As a result of blood loss incident to the original injury and the emergency operative procedure, and because of the somewhat impaired nutrition secondary to the altered bowel habits, the blood picture in most of these cases is somewhat below normal. From one to three transfusions have been required to restore a normal circulation before any type of closure is done. There is a week of preoperative preparation after the patient appears to be anatomically ready for closure. During this period the proximal and distal loops are irrigated daily with warm saline solution and an occasional enema is given. Since no succinylsulfathiazole is available in this area, 1 gm. of sulfaguanidine is administered every four hours during the week of preparation. A low-residue diet is given beginning four days prior to operation, and during the final twenty-four hours only clear fluids are given. Multi-vitamin preparations are given from admission until the patient has regained ability to tolerate a full diet postoperatively. A thorough cleansing of both loops of the colostomy is done on the evening before operation and again just prior to leaving the ward for the operating room.

Postoperative Care

On the patient's return from the operating room the following routine is employed. A transfusion of 500 cc. of whole blood is given immediately and is repeated if indicated. Drainage with a Wangensteen tube is done until flatus is being passed spontaneously and the abdomen is perfectly soft; this period averages three days. A dose of 3000 cc. of 5 per cent glucose in normal saline solution is given daily until the patient begins to take fluids, and in some cases 1000 cc. is given daily for one or two more days. Penicillin is administered, 40,000 units being included in each infusion.

The patient receives 16 mg. of morphine every four hours for the first day and as needed thereafter. On about the third day the suction tube is clamped

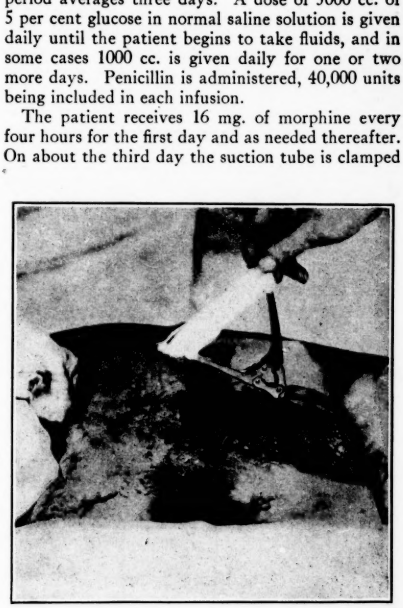

Figure 2. *An Abdominal Wound Caused by a Shell Fragment. The suture line of the exploratory incision has separated. There is a large defect in the lower abdominal wall opening directly into the abdominal cavity. A clamp has been applied to the colostomy spur. Note the extensive denuded area. Evacuation of the entire bowel drainage onto, and in fact into, this wound posed a difficult surgical and nursing problem.*

and the ingestion of small amounts of fluids by mouth is begun. If these are well tolerated, they are increased, and the patient is given a light diet for two days and then placed on a regular diet. There is usually normal defecation on the fourth day without an enema, and from then on convalescence is generally uneventful.

Results

In this series of 26 cases, closure failed in only 1. In this case a small localized abscess was encountered alongside the bowel and deep in the abdominal wall.

In the face of this fact, no further freeing of the bowel was done, but it was closed in the hope of eliminating the fecal drainage as an aid to clearing up the infection. Drains, of course, had to be inserted into the abscess cavity. This closure broke down and fecal drainage persisted, and it took several weeks to clear up the infection in the abdominal wall. The patient finally had to be evacuated with a persistent fecal fistula, but he was afebrile and had no urther suppuration and had normal bowel movements as well. Final closure will have to be postponed until all inflammatory reaction has subsided. The patient was, however, gaining weight and doing well generally when evacuated to the Zone of Interior.

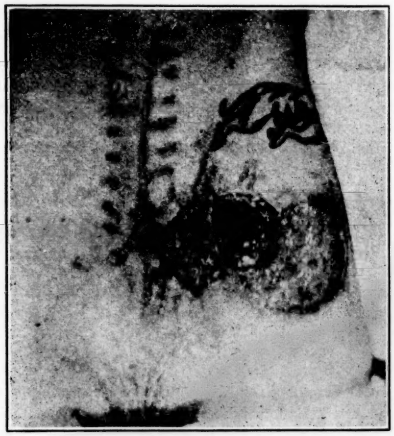

FIGURE 3. *Photograph of the Same Abdomen at an Intermediary Stage.*

The midline wound has healed. The spur has been cut through, ready for closure of the bowel. There is still a large denuded area, which could not be grafted because of continual soiling. At this point, the patient was operated on; the colostomy was closed, the abdominal wall was repaired, and the skin defect was covered with split-thickness grafts.

In 2 cases the wounds broke down slightly, with a small amount of fecal drainage for a few days. These wounds closed spontaneously, and there were no signs of peritoneal soiling.

There was 1 death in this series. It was caused by intestinal obstruction with massive gangrene of the bowel owing to adhesions resulting from the original trauma. The colostomy closure was functioning perfectly and was unrelated to the obstruction, which involved practically the entire small bowel, the latter being caught in multiple dense adhesions. This case will be discussed fully in a subsequent paper on intestinal obstruction following abdominal wounds with bowel injury.

In 23 cases there were no complications. All these patients ran an extremely mild postoperative course and immediately developed normal bowel habits. They gained in weight and made general improvement, and were returned to the Zone of Interior in excellent physical and mental condition.

The case history of a patient with extensive abdominal trauma illustrates some of the many problems involved in the management of these cases.

A 35-year-old private was wounded on December 21, 1944, by a shell fragment, which tore a large hole in the left lower quadrant of the abdominal wall. There had been evisceration of the ileum and jejunum, with perforation of the jejunum and of the sigmoid colon. He had, of course, experienced severe shock. On December 21, the jejunum was closed and the sigmoid exteriorized, and an unsuccessful attempt was made to close the abdominal wall.

The patient was evacuated to the United Kingdom on December 29, and was admitted to this hospital on January 2, 1945. The abdomen showed extensive loss of tissue (Fig. 2). The operative incision had completely broken open and was held only by deep stay sutures. The bowel could be seen moving beneath the incision with respiration. Abdominal fluid welled up freely through the wound. A dark triangular area just medial to the colostomy opened into the abdomen and was constantly filled with feces. An area over the left iliac crest was completely denuded of skin, and the whole wound exuded with pus and feces.

FIGURE 4. *The Final Result.*

The entire wound healed solidly, and normal bowel habits were restored. Note the skin grafts closing the defect seen in the previous illustrations.

The wound was strapped together with wide fenestrated strips of adhesive, and was flushed several times a day, after the abdominal cavity had been protected as much as possible with wide strips of vaseline gauze. Cutting of the spur was begun at once (Fig. 2). Several transfusions were given to build up the patient's general condition, and on January 9, under Sodium Pentothal anesthesia on the ward, a simple purse-string suture was applied to the colostomy in an at-

tempt to stop the fecal contamination of the open wound. This suture broke down in a few days. On January 17, a large abscess of the right thigh was drained. On January 30, pinch grafts were applied, and these stimulated the growth of points of epithelium that helped to close the wound. On February 24, a clamp was reapplied to cut the spur down a little more, and on March 5 preparation of the patient for closure of the colostomy was begun. There was still a large granulating area about the colostomy (Fig. 3), but an adequate lumen had been established. On March 12, under spinal anesthesia, the bowel was freed and closed by a transverse suture. It was possible to close the peritoneum over the sutured bowel without completely freeing the intra-abdominal adhesions. There was some difficulty in repairing the defect in the abdominal wall owing to loss of fascia, but a flap of the external oblique muscle was used to close the wound securely. Split-thickness skin grafts were then applied, all the denuded areas on both sides of the colostomy being included.

The patient did extremely well. There was a small amount of leakage, which closed spontaneously, and the wound healed solidly (Fig. 4). The patient developed normal bowel habits and gained in weight, and was returned home in excellent condition.

SUMMARY

The closure of colostomies in 26 cases following battle injuries is reviewed. Most of these were closed without resection and without completely freeing the bowel. In cases in which the local closure resulted in a lumen of questionable adequacy, an auxiliary stoma was made in adjacent loops. Thus, a satisfactory bowel continuity was re-established with a minimal sacrifice of blood supply and with a mild postoperative course.

In this series a fair amount of intraperitoneal walling-off has been encountered. The re-establishment of adequate bowel continuity and closure without disruption of this protective mechanism seemed to minimize the severity of the postoperative course and to offer some protection against leakage and soiling.

An interesting and difficult case is presented.

A NEW ANTISEPTIC SOLUTION FOR TOPICAL APPLICATION

Comparative In Vitro Studies

ETHAN ALLAN BROWN, M.R.C.S. (LONDON), L.R.C.P. (ENGLAND),* WILFRED KRABEK, M.Sc., AND RITA SKIFFINGTON, B.Sc.

BOSTON

THE earliest written records contain references to the use of germicidal agents.[1] The standard drug encyclopedias[2] list more than one hundred official and nonofficial preparations used for this purpose. The voluminous literature concerned with antiseptics attests to the intense study that has been given this subject, one of paramount importance in the field of medicine.

The ideal antiseptic for topical application must be stable, nontoxic, nonirritating and nonallergenic. It must act fairly quickly, yet its action in mixed infections must be relatively long lasting and effective. Its properties should permit its safe application to tissues as different as are the skin and mucous membranes, as well as to the highly specialized epitheliums of the eye and ear and, perhaps, of the genitalia. There must be no esthetic objections to its color, odor or other physical characteristics. Other considerations, such as availability and price, are secondary but nevertheless important factors.

With this and other points in mind, almost all available antiseptic solutions were studied and classified, but each was found wanting in one or more of the necessary qualifications. A review of the history of topical antisepsis reveals that one of the oldest of present-day solutions, hydrogen peroxide, possesses the greatest number of the above-listed advantages. Not only are its constituent and end products innocuous, but it is intimately related to bacterial metabolism.[3] It has fallen into disfavor because it suffers from two apparently major disadvantages: it is not stable in vitro, and its action in vivo is too transient to affect bacteria. The stabilization of hydrogen peroxide and the control of its rate of decomposition in catalase or peroxidase systems would open a new field in both peroxide chemistry and wound antisepsis.

It occurred to us that these problems could be solved by the use of carbamide peroxide as a solute and a source of hydrogen peroxide and that of anhydrous glycerol as a solvent. With the discovery that carbamide peroxide can be stabilized in alcohols and especially glycerol,[4] it seems that such solutions may have unusual antiseptic properties.

Studies of the action of 4 per cent carbamide peroxide in glycerol on fusiform bacteria[5] have shown that, by the agar-cup plate method, zones of inhibition are produced whose radial measurements from the edge of the cup to the edge of the zone are approximately 18 mm. A 0.125 per cent solution gives a zone of 5 mm. The glycerol control and the materials used for comparison — phenol (1 per cent), Pepsodent (undiluted) and Listerine (undiluted) — showed no zones of inhibition.

Further studies[6] demonstrated that following the oral use of carbamide peroxide solution (2 per cent in 50 per cent glycerol and 50 per cent water),

*Instructor in medicine, Tufts College Medical School; consultant in allergy, Joseph H. Pratt Diagnostic Hospital; physician-in-chief, Allergy Clinic, Boston Dispensary.

the total number of viable bacteria in the oral cavity was reduced by 26 to 93 per cent for a period of two hours. The viable fusiform bacteria were reduced by 52 to 93 per cent. The number of bacteria, both viable and nonviable, were reduced by 10 to 62 per cent.

The use of this solution in 35 cases of chronic purulent otitis media[7] gave the following results. Three patients showed no improvement, and 3 required additional treatment. The condition cleared completely in 29 cases within four to thirty-eight days, and in 17 cases within fourteen days. Equally encouraging results were achieved in the treatment of infections of the skin, eyes and mouth and in varicose and diabetic ulcers. These results will be reported in later articles. In all, the solution has been used by more than thirty physicians on more than 650 patients, in studies extending over a period of four years. The present paper, part of an extended series on antiseptics, is concerned with laboratory data, the solution being compared with a number of standard preparations for a series of organisms generally present in infections of the skin and mucous membranes.

The solution consists of 4 per cent carbamide peroxide in substantially anhydrous glycerol. Experiments with an 8 per cent solution are included, although its use in patients was followed on several occasions by slight transient irritation. For purposes of identification, the solution has been tentatively named Thenardol, in order that it may commemorate Jacques Louis Thénard (1777–1855), the discoverer of hydrogen peroxide.

On contact with water, the carbamide peroxide is split into carbamide (urea) and hydrogen peroxide. The presence of catalase or peroxidase in the tissues causes decomposition of the hydrogen peroxide into water and oxygen. In the concentrations present, none of the contained substances are toxic, irritating or allergenic.

The uses of urea as a peptizing agent are too well known to require listing.[8, 9] It should be noted at this point that all the previous studies concerning urea have dealt with its aqueous solution. Preliminary studies indicate that with the glycerol solution there is little or no absorption from wide areas of denuded tissues and no rise in nonprotein nitrogen.

The literature concerned with the antiseptic effects of hydrogen peroxide covers a period of more than sixty years; the greater part of it is unfavorable.[10] Many of the authors who have worked in this field have noted that its relative ineffectiveness is chiefly due to its rapid decomposition and therefore transient action in aqueous solutions. None of this literature is pertinent, since little previous work has been reported regarding the action of hydrogen peroxide in glycerol, in which the rate of decomposition is relatively slow. Noteworthy work has been done by Meleney,[11] who since 1935 has worked with slow-acting peroxides, especially zinc peroxide, in watery suspensions, and by Reid and Altemeier,[12] who used the same peroxide in ointment form. The latter investigators state that the organic peroxides tend to be unstable but that urea peroxide in ointment form, if carefully made, remains stable. No details of the process of preparing the ointment are given. Our technic of preparation gives us an organic peroxide in stable liquid systems.[4]

The biochemistry of glycerol has been reviewed in detail.[13] It has been stated[14] that it is used more frequently in prescriptions than is any other substance except water. The ingestion of 30 cc. three times daily for fifty days by 14 normal adults was found to be harmless.[15] It should be noted that the absorption of glycerol, a factor to be considered in its application to large denuded areas, especially in diabetic patients, leads to the formation of glucose and glycogen.[16]

Although experimental work with wounds in animals[17] has shown that glycerol holds granulations in check and permits epithelium to advance, not all authorities agree that this is clinically true. Glycerol solutions are said to cause irritation, owing in most cases to their dehydrating properties.

The term "irritation" requires definition so as to make it clear whether it refers to the subjective feelings of the patient or to the objective observations of the investigator. It is also necessary to consider the length of time the antiseptic solution has been used and the type of lesion to which it has been applied. Almost all substances, including water, retard healing if left in contact with damaged tissue for a sufficiently long time.

In 4 of our patients, there were complaints of a burning sensation but no objective changes could be seen. In another patient, no irritative effects were noted until the solution had been used as a continuous wet dressing on an infected anterior abdominal wall for fifty days.

It appears from preliminary clinical studies that glycerol solutions, although irritating at the point in the patient's progress at which the infection is under control and exudate is at its minimum, are less irritant than are any of the antiseptic tinctures that the physician is likely to use, either prophylactically or therapeutically, for the same type of lesion at the same time. Irritation is of concern only when it occurs before the infection has been checked. When it does so at a later date, it merely gives warning that the antiseptic should have been discontinued, however difficult it is to choose the moment at which this should be done.

In the present solution, the hygroscopic property of the glycerol constitutes a valuable adjunct to the chemotherapeutic process, since it draws plasma from the deeper parts of wounds, thereby washing out micro-organisms and exposing them to antiseptic action. Its viscosity gives it the mechanical

advantage of both the liquid and ointment types of medication. One of the special virtues of the solution is that it does not dry when used as a wet dressing in chronic infections.

Our studies were concerned with more than one hundred antiseptic solutions, of which the following six, used for comparison, were chosen for the present paper: tincture of iodine (*U.S.P.*), Tincture of Mercresin (standard strength), Mercurochrome (2 per cent aqueous), Tincture Metaphen (1:200), Tincture of Phemerol (1:1000) and Zephiran Chloride Tincture (1:1000). The list includes a halogen, two mercurials, a mercury-phenolic compound and cationic agents dispensed as tinctures and as aqueous and glycerol solutions.

We appreciate the fact that 2 per cent aqueous Mercurochrome is not the vehicle in which the substance is said to show its greatest effects. Since it and the other solutions listed have been the subjects of study in all the forms in which they are available and will be reported in detail separately, mercurochrome was chosen as representative of an aqueous mercurial widely used for its supposedly antiseptic action.

These studies were concerned with the effects of antiseptic solutions on approximately forty pathogenic organisms, of which the following twelve are covered in this report: *Staphylococcus aureus* (FDA, Strain 209, and our own laboratory strain); alpha-hemolytic and beta-hemolytic streptococci; an enterococcus; *Micrococcus epidermidis*; a diphtheroid; *Proteus mirabilis*; *Pseudomonas pyocyaneus*; *Escherichia coli*; *Aerobacter aerogenes*; and *Eberthella typhosa*. The first seven organisms are gram-positive, and the remaining five are gram-negative.

The testing method used was a modification of the FDA agar-cup plate technic.[18] Bacto dextrose agar, 35 cc. (pH 7.3), was inoculated with 0.2 cc. of a twenty-two-hour to twenty-six hour dextrose broth culture of the organism to be studied and poured into a 90-mm. petri dish with an unglazed porous top. After the agar had hardened, a 1.5-cm. cup was cut with a sterile cork borer, and a drop of melted agar was introduced into the cup to fill any cracks present. With a sterile pipette, 0.2 cc. of the antiseptic to be studied was placed at the bottom of the cup. Replicate experiments were performed three or more times for each solution and for each strain. The results were consistent within significant limits.

The plate was immediately incubated at 37°C. and read after eighteen hours. Approximately 0.25 sq. cm. of the medium was removed for subculture, being taken at a point 2 to 5 mm. in from the edge of the clear zone.

Dextrose agar was chosen as the medium so that maximum growth might be achieved for the greatest number of species with uniform conditions for all. Brewer's thioglycollate medium was chosen for the subcultures, since it detoxifies the mercurials and counteracts any residual peroxide. It seemed to have little or no effect on the cationic solutions, such as Zephiran. Considering the number of subcultures necessitated by this work and the relatively small zones obtained under the conditions of the experiments, the use of cationic detoxicants of the type mentioned by Valko and DuBois[19] was not considered feasible.

The clear zone was measured radially in millimeters from the outside edge of the cup to the edge of the clear zone. When the zones were irregular in outline, five representative measurements were taken and an average figure was determined. When the zone edges were hazy, the exact zone was determined by subcultures taken

TABLE 1. *Measurement of Antiseptic Potency by a Modified Agar-Cup Plate Method.**

	Organism	Antiseptic								
		Tincture of Iodine (*U.S.P.*)	Thenardol (8%)	Thenardol (4%)	Tincture Metaphen (1:200)	Tincture of Mercresin (standard strength)	Mercurochrome 2% (aqueous)	Zephiran Chloride Tincture (1:1000)	Tincture of Phemerol (1:1000)
		mm.	mm.	mm.	mm.	mm.	mm.	mm.	mm.
A	*Staph. aureus* (FDA, Strain 209)	19	19	18	(16)	(19)	(9)	11	9
B	*Staph. aureus* (lab. strain)	20	17	12	(11)	(19)	(7)	10	(7)
C	Streptococcus (alpha-hemolytic)	28	22	20	11	(15)	6	8	10
D	Streptococcus (beta-hemolytic)	13	18	16	13	(15)	(6)	2	(3)
E	Enterococcus	18	18	15	22	11	(3)	6	(3)
F	*M. epidermidis*	22	17	11	9	12	6	(8)	8
G	Diphtheroid	22	24	(18)	11	(16)	6	(16)	5
H	*P. mirabilis*	13	17	16	(11)	(9)	(5)	(1)	(1)
I	*Ps. pyocyaneus*	21	16	15	(12)	(12)	(6)	4	(5)
J	*Esch. coli*	9	11	10	(13)	9	(6)	(1)	(1)
K	*A. aerogenes*	23	12	12	9	11	5	6	(2)
L	*E. typhosa*	24	16	14	25		5	(2)	(2)

*The measurements are given in millimeters from the edge of the cup to the edge of the zone. The numbers in parentheses refer to the zones that gave positive subcultures and imply that the antiseptic solution at the point of subculture was bacteriostatic but not bactericidal.

from the center of the plate toward the periphery. The results are listed in Table 1.

We are fully cognizant of the fallacies inherent in the conclusions that can be drawn from the type of test described. These have been ably discussed by Nye,[20] many of whose suggestions have been taken into consideration in this and the subsequent papers of the present series. The test is, however, a standard one. It does not control the effects of sublimation and so-called "creeping" for tincture of iodine and of creeping alone for other tinctures. The inhibitions produced by such solutions therefore suggest greater effectiveness than do exact measurements of actual bactericidal action, thus showing them to their greatest advantage.

and 4 per cent Thenardol. The letters below the columns identify the organisms, according to the listing in Table 1. The negative sign (—) over a solid column evidences a negative subculture 2 to 5 mm. central to the edge of the zone and implies that the column represents the zone of bactericidal power. An open column indicates that subcultures were positive and implies that the antiseptic was bacteriostatic rather than bactericidal. Subsequent reports will deal with the exact limitation of such zones of bacteriostasis, subcultures being taken radially at 2-mm. intervals from the edge of the cup to the edge of the clear zone.

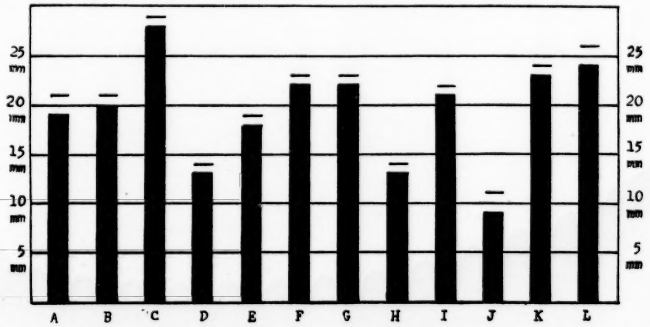

FIGURE 1. *The Measurement of the Effects of Tincture of Iodine* (U.S.P.) *on Twelve Common Organisms.*

It will be seen from the tables that tincture of iodine gives the largest zones. As noted above, the control of these qualities results in zones greatly reduced in size. Since this work has not become generally known, the traditional method has been used for the present paper.

The accompanying charts (Figs. 1 and 2) demonstrate the results for tincture iodine (*U.S.P.*) with correction for the effects of sublimation and creeping these zone are reduced in size by 2 to 20 mm. The factors involved are varied and complex and require separate studies. This fact holds equally true for the other tinctures, although to a lesser extent.

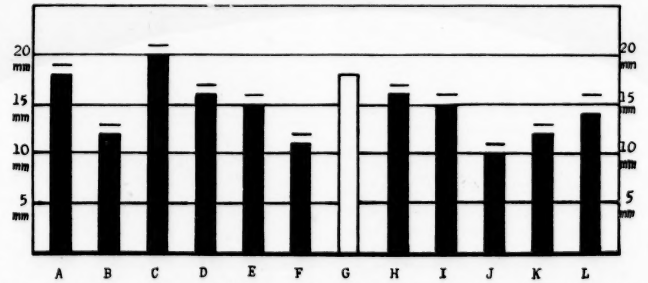

FIGURE 2. *The Measurement of the Effects of Thenardol* (*4 per cent*) *on Twelve Common Organisms.*

The differences in effect on the members of the gram-positive (A-G) and the gram-negative (H-L) groups by the antiseptic solutions, especially the cationic detergents, as shown in Table 1, is worth noting. The antiseptics have been arranged in the approximate order of potency, as measured by the agar-cup plate method. As noted above, the measurements were taken radially from the edge of the cup to the edge of the zone in millimeters. Whenever subculture material was positive, the zone was considered one of bacteriostasis. In this event the measurements are enclosed in parentheses. Otherwise, the measurements refer to zones of bactericidal effect as proved by negative subcultures.

Since replicate experiments showed the behavior of the antiseptic solutions to be consistent for each organism, the inconsistent effects of differing organisms should be noted. Tincture of iodine and 8 per cent Thenardol demonstrated excellent bactericidal power. With 4 per cent Thenardol there were positive subcultures for the diphtheroid group. Tincture Metaphen appeared to be bacteriostatic for the staphylococci used and, in the gram-negative group, for *P. mirabilis*, *Ps. pyocyaneus* and *Esch. coli*. Tincture of Mercresin was bacteriostatic for seven of the bacteria, the subcultures being negative for the enterococcus, *M. epidermidis*, *Esch. coli* and *A. aerogenes*. For technical reasons, the results for *E. typhosa* have been omitted, the zone having been too irregular to be read with accuracy. Mercurochrome gave small zones for all the organisms, with positive subcultures for seven. Its effects were apparently less uneven than those of the other solutions studied. The action of Zephiran Chloride Tincture was extremely irregular, with little or no demonstrable effect on *P. vulgaris*, *Esch. coli* and *E. typhosa*. Tincture of Phemerol showed almost no bactericidal power for nine of the twelve bacteria. It affected the standard staphylococcus but not the laboratory strain, a much more resistant organism.

If tincture of iodine is taken as a standard, the great difference between its bactericidal power and those of the other solutions studied is quite remarkable and should do much to outweigh its irritant, toxic and allergenic properties, especially since the mercurials are themselves not free of these same faults. The agar-cup plate technic therefore appears to corroborate the previous studies, especially those of Nye,[20] who reached the same conclusions although using other technics in the evaluation of iodine solutions. Since iodine cannot, however, be used either for applications at frequent intervals or for continuous wet dressings, search for other solutions possessing some of its qualities and adapted for these uses must be made.

Summary

The composition and properties of a new antiseptic solution that is neither toxic, irritant nor allergenic are described. A comparison between it, tincture of iodine and five commercial antiseptic solutions by the agar-cup plate method, with the use of twelve commonly occurring micro-organisms, demonstrates its bactericidal efficacy. Its chemical, physical and bactericidal properties seem to commend its use in mixed infections of the skin and mucous membranes.

Although the perfect antiseptic for topical application in mixed wound infections has not yet been discovered, carbamide peroxide in glycerol or similar solutions appears to approach this goal.

References

1. Goodman, L., and Gilman, A. *The Pharmacological Basis of Therapeutics: A textbook of pharmacology, toxicology and therapeutics for physicians and medical students*. 1383 pp. New York: The Macmillan Company, 1941.
2. Gutman, J. *The Modern Drug Encyclopedia*. 1644 pp. New York: The American Journal of Surgery, Inc., 1941.
3. McLeod, J. W., and Gordon, J. Production of hydrogen peroxide by bacteria. *Biochem. J.* **16**:499-506, 1922.
4. Brown, E. A., Abramson, H. A., Gorin, M. G., Kauffmann, H. O., and Shanley, E. S. Stability of urea peroxide in alcohols. To be published.
5. Brown, E. A., and Slanetz, L. W. Germicidal action of carbamide peroxide in glycerol on fusiform bacteria. To be published.
6. *Idem*. Diminution of number of oral organisms following use of carbamide peroxide in glycerol. To be published.
7. Brown, E. A., and Owen, W. E. Treatment of chronic purulent otitis media with carbamide peroxide in glycerol. *Arch. Otolaryng.* To be published.
8. Robinson, W. Use of urea to stimulate healing in chronic purulent wounds. *Am. J. Surg.* **33**:192-197, 1936.
9. *Idem*. Stimulation of healing in non-healing wounds by allantoin occurring in maggot secretions and of wide biological distribution. *J. Bone & Joint Surg.* **17**:267-271, 1935.
10. McCulloch, E. C. *Disinfection and Sterilization*. Second edition. 472 pp. Philadelphia: Lea & Febiger, 1945.
11. Meleney, F. L. Zinc peroxide in treatment of micro-aerophilic and anaerobic infections, with special reference to group of chronic, ulcerative, burrowing, non-gangrenous lesions of abdominal wall apparently due to micro-aerophilic haemolytic streptococcus. *Ann. Surg.* **101**:997-1011, 1935.
12. Reid, M. R., and Altemeier, W. A. Peroxide ointments. *Ann. Surg.* **118**:741-750, 1943.
13. Deonhman, W. Glycerol: behavior in animal organism (review of literature). *Indust. Med. (Indust. Hyg. Sect.)* **1**:60-67, 1940.
14. Lesser, M. A., and Murphy, J. R. Survey on users of glycerol. *Am. Profess. Pharmacist* **2**:18 (June); 20 (July); 22 (August), 1936.
15. Schubel, K. Zur Pharmakologie des Glycerins. *Sitzungsb. d. phys.-med. Soc. zu Erlangen* (1935-1936). **67-68**:263-266, 1937.
16. Noble, E. C., and MacLeod, J. J. R. Influence of sugars and other substances on toxic effects of insulin. *Am. J. Physiol.* **64**:547-560, 1923.
17. Sutton, L. E. Thioglycerol: more stable sulphydryl compound for use in healing of wounds. *J. A. M. A.* **104**:2168-2171, 1935.
18. *U. S. Food and Drug Administration Methods of Testing Antiseptics and Disinfectants*. Circular 198, 1931.
19. Valko, E. I., and DuBois, A. S. Antibacterial action of surface active cations. *J. Bact.* **47**:15-25, 1944.
20. Nye, R. N. Relative in vitro activity of certain antiseptics in aqueous solution. *J. A. M. A.* **108**:280-287, 1937.

PAPILLOMA OF THE GALL BLADDER*

DAVID MILLER, M.D.†

NEW YORK CITY

IN THE general problem of biliary disease, the relatively infrequent occurrence or recognition of papilloma of the gall bladder is of interest. This report was prompted by the recent finding of 3 cases within the last few months. In each case the preoperative diagnosis was correctly made by the roentgenologist.

Estimations of the frequency of occurrence of papillomas vary, depending on the criteria for histologic diagnosis of these tumors. Kerr and Lendrum,[1] whose criteria were most exacting, had accepted only 7 cases up to 1936. To these was added a case reported by Brown and Cappell[2] and accepted by the previous authors. On the other hand, in the American literature, Irwin and MacCarty[3] found 85 cases of papilloma of the gall bladder in 2168 cases of gall-bladder disease, and C. H. Mayo[4] found 107 cases in 2538. Kirklin[5] reported an incidence of 8.5 per cent of gall bladders containing one or more papillomas in 1700 patients undergoing cholecystectomy at the Mayo Clinic during a period of about six years. Recently, Greenwald[6] reported a series of cases similar to those discussed below.

Although polypoid lesions of the colon and the urinary bladder have a significant association with carcinoma of these organs, this does not appear to be important in the present connection. Phillips[7] in his series of 500 cases found 1 case in which carcinoma occurred in a papillomatous gall bladder. Kerr and Lendrum[1] reported 3 cases of carcinoma in patients who had gall bladders containing papillomas. I am not aware of any other similar cases.

In the following cases, the abdomen was surgically explored and the gall bladder was removed because of the presenting symptoms, rather than because of the possibility of cancer. The latter can never be ruled out, however, without histologic examination. It is not unreasonable to expect that in rare cases an early carcinoma near the fundus of the gall bladder will be found in cases in which the preoperative diagnosis is papilloma.

CASE REPORTS

CASE 1. A. K. W. (DH-40999), a 36-year-old, married woman, was admitted on July 27, 1944, complaining of attacks of nonradiating pain in the right upper quadrant of the abdomen of 3 years' duration. The attacks occurred at 2-month intervals and followed the ingestion of fatty or fried foods. There had been no fever, chills or jaundice. Twelve years previously, the patient had a cesarean section. She had had no other operations and no significant illnesses.

Physical examination was essentially noncontributory. Roentgen-ray examination by Dr. Alice Ettinger at the Pratt Diagnostic Hospital, Boston, revealed papillomas of the gall bladder.

The patient was operated on by Dr. Ralph Colp. Exploration of the abdomen revealed a gall bladder of normal size with a slightly thickened wall. Cholecystectomy and appendectomy were performed.

Gross examination of the mucosal surface of the gall bladder showed four papillomas, each 0.5 cm. long, attached by thin pedicles. They were the same color as the rest of the mucosa and somewhat translucent. Microscopic examination of these tumors showed tufts of thin stroma lined with columnar cells (Fig. 1), some of the tufts were stuffed with large clear lipoid-bearing cells. The surface epithelium of the gall bladder mucosa was otherwise normal. The wall of the organ showed an increase in fibrous tissue and round cells. The appendix was normal on gross and microscopic examination.

FIGURE 1. *Case 1.*

A low-power photomicrograph showing the papilloma attached by a thin pedicle to the mucous membrane of the gall bladder.

The patient was relieved of her symptoms and made an uneventful recovery.

CASE 2. D. B. (DH-42485), a 46-year-old, married man, was admitted in November, 1944, complaining of attacks of pain in the right upper quadrant of the abdomen, radiating to the right shoulder and scapular region, of several months' duration. For an indefinite period of time he had had postprandial distress and flatulence. On rare occasions he had had some nausea and vomiting. He had never had fever or jaundice with attacks of pain. The past history revealed nothing of importance except hay fever.

Physical examination was essentially normal except for slight tenderness in the right upper quadrant. Roentgenograms of the gall bladder were interpreted by Dr. Arthur Bendick as showing papillomas.

*From the Surgical Service of Dr. Ralph Colp, Mount Sinai Hospital.

†Adjunct surgeon, Beekman Hospital; member of staff, out-patient department, surgical clinic, Mount Sinai Hospital.

Exploratory laparotomy was performed by Dr. Ralph Colp on November 9. The gall bladder was distended with dark-green bile and contained several stones. When it was removed and opened, it was seen to contain two papillomas 1 cm. in length. Microscopically, these consisted of piled-up villi with a thin fibrous core lined with columnar epithelium (Fig. 2). The wall of the gall bladder and the mucous membrane were otherwise normal. The common duct was not dilated and contained no palpable stones. There were no other abnormalities.

FIGURE 2. *Case 2.*
A low-power photomicrograph showing the papilloma, which has complex processes.

The patient recovered from the operation uneventfully and has been well to the present.

CASE 3. J. M. (MSH–431865), a 35-year-old man, who was admitted in March, 1945, had had vague episodes of dyspepsia over a period of 8 months. These were unrelated to the ingestion of any particular foods. Three weeks before admission he had an attack of epigastric pain, which was relieved by the repeated belching of gas. Similar attacks ensued at irregular intervals. Six hours before admission, non-radiating epigastric pain and distress began and persisted. There was no vomiting.

On physical examination there was moderate tenderness in the right upper quadrant of the abdomen. The patient was afebrile. No mass was palpable. The white-cell count was 16,000, with 90 per cent neutrophils.

The patient was given intravenous glucose and saline solution, and the symptoms subsided within a few hours. Subsequent roentgen-ray examination of the gall bladder showed two radiotranslucent areas, which did not shift in position as the patient was moved (Fig. 3). Dr. Marcy Sussman's diagnosis was papilloma of the gall bladder.

The patient was operated by Dr. Ralph Colp on March 20, 1945. The gall bladder was thin-walled. The stomach was normal. The gall bladder was removed and opened, and two papillomas of split-pea size were seen on the mucous membrane, to which they were attached by thin pedicles. There was an elevated area of mucous membrane 0.5 cm. in diameter above the surface of the mucosa. There were also present two bright-orange excrescences 1 to 2 mm. in diameter. There were no stones.

The patient has remained well since operation.

DISCUSSION

The etiology of these tumors is a matter for speculation. Infection may play a significant part. Of the 500 cases reported by Phillips,[8] 255 (51 per cent) occurred in association with chronic catarrhal cholecystitis. In contrast to carcinoma of the gall bladder, the presence of stones in papilloma of the gall bladder seems to have no etiologic significance. Stones were present in 26.8 per cent of Phillips's series. Carcinomas of the gall bladder are associated with stones in 65 per cent to 90 per cent of various series. Polypoid excrescences occur in the so-called "strawberry" gall bladder. These contain deposits of cholesterol, discernible to the naked eye as yellow masses. Such masses may form the nuclei for stones.

Phillips[8] states that infection and metabolic disturbances, often working together, may play a role in the etiology of these tumors. The nature of the metabolic disturbance is not clear. In a number of cases described by him, papillomas were present in a strawberry gall bladder.

The papillomas appear as projections from the mucous membrane of the gall bladder. Their color is that of the mucous membrane. The pedicles may be so thin that the new growth is easily brushed off or so broad that the mass is firmly attached. These projections may appear in any portion of the organ, but they occur oftenest at its neck or midportion. Microscopically the growths consist of branching complex processes of thin stroma lined with columnar cells.

In the large series of reported cases, the majority of cases usually occur after the third decade of life. The ages in the present cases were thirty-five, thirty-six and forty-six years, respectively.

The symptoms that bring the patient under observation are similar to those of chronic cholecystitis. Intolerance to fatty or fried foods, dyspepsia, flatulence and attacks of pain in the epigastrium and right upper quadrant of the abdomen occur. Fever, chills and jaundice are not usually noted. The patient comes to operation at any time from months to years after the onset of symptoms. It is not clear why these papillomas, often unassociated with stones or infection, produce symptoms. One is forced to indict a vague metabolic disturbance as a causative agent. Relief of the symptoms is obtained by cholecystectomy.

The preoperative diagnosis can be readily made with a high degree of assurance by roentgen-ray examination. In a series of 15 cases of papilloma, Kirklin[5] was able to diagnose 14 preoperatively. He states that the best time for examination is the twentieth hour after the ingestion of dye. Stones usually change their position with succeeding examinations, are often bunched together and are most frequently found at the fundus. Most papillomas are discrete, do not change position and are

rarely found at the fundus. Adenomas are usually larger than papillomas, measuring 2 cm. or more in diameter, as against 0.5 cm. to 1.0 cm., and are frequently present at the fundus. Sarcomas are exceedingly rare, only 13 cases having been recorded in the literature.

Since the majority of carcinomas arise near the neck of the gall bladder, the organ is obstructed and damaged and cannot be accurately visualized.

When the papillomas give rise to symptoms, the treatment is surgical. Cholecystectomy should be performed, since it gives relief. Unless jaundice has been noted preoperatively or operation reveals a dilated common duct with an intrinsic palpable mass or many small stones, the common duct need not be opened. Colp[11] pointed out in a recent paper that between 30 and 40 per cent of cholecystectomized patients have attacks of pain similar to those

FIGURE 3. *Case 3.*
Gallbladder at twenty-one hours filled with dye and showing two faint translucent areas.

Sosman,[9] in his recent excellent paper on the radiologic aspects of gall-bladder disease, stated that he had never made a diagnosis of carcinoma of the gall bladder by cholecystography. Furthermore, Sussman[10] does not recall having made such a diagnosis. For details of the technic of cholecystography, the papers by Sosman[9] and Kirklin[5] should be consulted.

that preceded operation. These attacks usually occur within two years of the operation and may be temporary. In cases in which stones had been present, this postcholecystectomy syndrome was encountered less frequently.

CONCLUSIONS

Papillomas of the gall bladder are infrequent and are rarely associated with carcinoma. They may

give rise to symptoms similar to those of chronic cholecystitis, and can be diagnosed preoperatively by roentgen-ray examination.

If troublesome symptoms are present, cholecystectomy should be performed.

17 East 96th Street

References

1. Kerr, A. B., and Lendrum, A. C. Chloride-secreting papilloma in gall-bladder: tumour of heterotopic intestinal epithelium containing Paneth cells and interochromaffine cells and associated with massive chloride loss: with critical review of papilloma of gall-bladder. *Brit. J. Surg.* **23**:615-639, 1936.
2. Brown, F. R., and Cappell, D. F. Multiple villous papillomata o gall-bladder. *Brit. J. Surg.* **23**:703-707, 1937.
3. Irwin, H. C., and MacCarty, W. C. Papilloma of gall-bladder. *Ann. Surg.* **61**:725-729, 1915.
4. Mayo, C. H. Papillomas of gall-bladder. *Ann. Surg.* **62**:193-196, 1915.
5. Kirklin, B. R. Cholecystographic diagnosis of papillomas of gall-bladder. *Am. J. Roentgenol.* **1**:46-50, 1931.
6. Greenwald, W. Papilloma of gall bladder. *Surgery* **16**:370-376, 1944.
7. Phillips, J. R. Papilloma of gall bladder. *Proc. Staff. Meet., Mayo Clin.* **7**:578, 1932.
8. *Idem.* Papilloma of gall bladder. *Am. J. Surg.* **21**:38-42, 1933.
9. Sosman, M. C. Radiologic aspects of gall-bladder disease. *New Eng. J. Med.* **31**:786-793, 1944.
10. Sussman, M. Personal communication.
11. Colp, R. Postcholecystectomy syndrome and its treatment. *Bull. New York Acad. Med.* **20**:203-219, 1944.

MEDICAL PROGRESS

DIABETES MELLITUS (Concluded)

ELLIOTT P. JOSLIN, M.D.*

BOSTON

Diabetes in Children

Lichtenstein,[49] of Stockholm, has reported his ten years' experience in the treatment of diabetes in children without dietetic restrictions and appends the literature on this method of treatment from Stolte to Tolstoy. Following a review of his article, certain comments that seem pertinent will be given.

Lichtenstein has treated diabetic children for thirty-five years, the first fifteen years falling within the pre-insulin era, with its hopeless prognosis; he then changed to the customary strict low-carbohydrate diet and insulin, but gradually adopted a diet richer in carbohydrate but still limited, and for the last ten years he has used what he terms a "free diet." With this background he considers himself justified in stating that diabetic children, as a general rule, should be treated without any dietetic restrictions whatsoever. Various excerpts from Lichtenstein's article follow that suggest that the diets were not quite so unregulated as the title of the paper indicates. Attention is called to the meticulous care that his patients received in the hospital and at home. One wonders whether in the homes the mothers always combated polyuria and pruritus simply by increasing the dose of insulin without at the same time decreasing the carbohydrate in the diet.

Lichtenstein was led to adopt the free diet because, as he writes, a study of the history of diabetes diet shows that there are no definite scientific bases for a diet composed in a certain particular way. If there had been such, he points out, this diet would have superseded all others. He goes on to state that as years have elapsed since the introduction of insulin, the diet that had previously been extremely restrictive, especially in regard to carbohydrate, has in most places become more generous. He adds, "Most diabetes therapeutists, however, have so far hesitated to take the decisive step of changing over to a quite normal dietary."

In 1932, without previous knowledge of the work of Stolte, who was the first to advocate the treatment of diabetes in children without any dietetic restrictions, Lichtenstein began a free diet on a minor scale, and since 1933 he has treated his child patients without dietetic restriction. He considers this advantageous because children have long to live, have a more labile metabolism than do diabetic adults, with their sudden oscillations between hyperglycemia and hypoglycemia, — a perpetual menace of ketosis, — are more liable to infection and, owing to their growth and development, require an adequate supply of food. Furthermore, he believes that a free diet avoids placing children in a psychologic position apart from other children and thus prejudicing their development. Yet he also writes, "Adult diabetics need only be maintained in equilibrium and can even periodically be kept with advantage on a somewhat low diet." In this connection one is reminded of the biblical saying, "Bring up a child in the way he shall grow, and when he is old he will not depart therefrom," because the expectation of life for the diabetic child today is such that four fifths of it will be passed as an adult.

Lichtenstein apparently insists that, at first, all children are admitted to the hospital for treatment. Six specimens of urine are examined daily, tests are made of the blood sugar and volume of urine, and attention is paid to the insulin dosage and to possible acetonuria. The patients are kept under control in the diabetic outpatient department fol-

*Clinical professor of medicine, emeritus, Harvard Medical School; medical director, George F. Baker Clinic, New England Deaconess Hospital.

lowing discharge, or are followed in their homes by visits at intervals of a week to a few times a year. Lichtenstein describes his method of treatment as follows:

> Fresh cases receive from the outset "free diet." [By this Lichtenstein means a diet completely corresponding with that of healthy children.] The diabetic children are allowed at first to take the ordinary hospital fare and eat their fill. In their homes they are then allowed to share the diet of their brothers and sisters and playmates and to satisfy their individual taste within the same limits as for healthy children. Even sugar and sweets in reasonable amounts are permissible. At the hospital the amounts of food which the children *spontaneously* consume are weighed and measured. In their homes no weighing or measuring of the food is required. The only restriction made is to avoid overindulgence, a rule that should apply in equal degree to all children, thus also to healthy ones.
>
> The children receive the amount of insulin required to produce a good general condition, a feeling of well-being, a satisfactory increase in weight, a moderate amount of urine and complete freedom from acids in the urine. On the other hand, I attach less importance to a moderate rise in blood sugar and to a moderate or small excretion of sugar, in itself. Indeed, I prefer some excretion of sugar to complete freedom from sugar in the urine, as one then runs a smaller risk of hypoglycemia and ketosis, the two dangers that in the first place menace the diabetic child.
>
> The transition between dietetic treatment and "free diet" could always be made without difficulty. . . . Thus children who had previously received a diet of less than 100 gm. of carbohydrate per day, during the first few days of the "free diet" consumed 250 to 300 gm. of carbohydrate per day. After a few days, however, they spontaneously adjusted themselves to a more moderate consumption of carbohydrates, which, however, was always considerably higher than the amount previously permitted. As a rule it was about 150 to 250 gm. per day, corresponding to 6 or 7 gm. per kilogram of body weight.
>
> These children spontaneously consume as a rule 2 or 3 gm. of protein and 2.5 to 3.5 gm. of fat per kilogram per day.
>
> The supply of calories was as a rule spontaneously maintained at 80 to 100 for children under five, at 60 to 80 at the age of five to ten years and at 40 to 60 at the age of ten to fifteen years, all per kilogram of body weight.

The general condition of the patients is recorded throughout as extremely satisfactory, with no increased hunger, thirst or polyuria. They are said to have had a feeling of well-being and joy of life, in contrast to the regime that marked them out from healthy children. Growth in height and weight, with a few isolated exceptions, were well within the normal limits for healthy children in Sweden. No difficulties were encountered during puberty. As regards the carbohydrate metabolism, the presence of sugar in the urine up to some tens of grams of sugar for twenty-four hours was not considered a cause for concern provided that the patients felt well, and showed no increase in hunger or thirst, polyuria or itch. As a rule, the degree of glycosuria was less than 10 per cent of the carbohydrate intake. As a result of these measures, severe attacks of hypoglycemia were, in fact, extremely rare.

The blood-sugar fasting values in most well controlled cases ranged between 100 and 200 mg. per 100 cc.

Lichtenstein believes that the patients reacted better to infections than they did on the previously restricted diets. There was only 1 death from miliary tuberculosis, and of 41 patients who sooner or later showed a positive tuberculin reaction, only 1 developed a lung focus, and this healed. Neither increase in blood pressure nor demonstrable calcification of the blood vessels was observed. The cholesterol, as a rule, was below 230 mg. per 100 cc. In 1 case there was a slight unilateral cataract, and in a number of cases there was a slight transient enlargement of the liver.

Lichtenstein's mortality was low. Of the 169 patients, only 8 died. One was murdered, 1 succumbed to miliary tuberculosis with meningitis a few months after the onset of diabetes, 1 died of pleural empyema with peritonitis and one of scarlet fever, 1 died of oral infection, and 3 died of coma. The mortality rate for the ten-year period was 4.7 per cent. Lichtenstein compares this rate with that of my cases, as reported by White,[50] which was 8 per cent for 150 cases of fifteen years' duration. A comparison to be valuable should be made between children with similar durations of diabetes. It should be added that the mortality of this clinic will be still higher in the 249 cases that are of twenty years' duration and are soon to be reported.

Hagedorn's protamine insulin was used in Lichtenstein's cases instead of protamine zinc insulin. The dosage varied between 10 and 120 units a day, the average being about 40 units. The maximum dose of regular insulin averaged about 60 units. Lichtenstein also frankly points out:

> To obtain good results, one must exercise a careful, continuous control, with at first frequent and gradually more occasional examinations. In the case of children, the control involves good co-operation with the homes, especially with the mothers. It is therefore necessary to give instructions to the mothers. They must learn the principal features in the clinical treatment of the disease, they must learn to recognize, in particular, such changes in the child's condition as require a modification of the insulin dosage, and they must learn to use the insulin syringe correctly. Many mothers in our Swedish clientele can be taught to make qualitative and sometimes also quantitative sugar tests and even to perform Gerhard's and Legal's tests for ketone bodies in the urine. A more important matter, however, is to draw their attention to the significance of *greater thirst* and *large amounts of urine* as indications of unsatisfactory adjustment, and to the importance of immediately getting in touch in such cases with the doctor treating the case. Another important matter is to get the mothers to understand the *signs of hypoglycemia* and how it is counteracted. The importance of a *regular conduct of life* with regular meals should also be strongly emphasized.

My own aversion to the treatment advocated by Lichtenstein arises not so much from the actual diets that he employs — which, as a matter of fact, differ little from the average diet now generally given to diabetic children — as from the psychologic effect on the children and the parents of growing up with the belief that their diabetes can be controlled by insulin and not by diet, insulin and exercise. It is the old, old story — a compromise with evil that a possible good may come. Seneca wrote, "We may lay it down as an invariable axiom in all high education that it is never sensible to permit what is bad for the supposed sake of preventing what is worse." In the education of his pupil Nero,

so good a man as Seneca adopted this course but the world knows with what disastrous results. There is unanimous belief among my group that the children who have been treated with great care on a diet including 150 to 200 gm. of carbohydrate and who have endeavored to control their diabetes are the ones who have done the best and have avoided the most complications. I know — and my colleagues agree with me — that the patients who have lived on free diets but have admittedly tried less earnestly to control themselves with insulin have been the ones most frequently admitted to the hospital for coma and hypoglycemia. The extremes of such cases will not be included in our twenty-year group, soon to be reported, because these patients are already dead — they did not live even for twenty years.

Long ago I found on visits to noted diabetic clinics in this and other countries that the physicians in charge were skilled clinicians and treated their patients individually and with good results. These clinicians might advocate particular methods of treatment, but in their own clinics they were alive to the individualization of the patient and adjusted the diet and the giving of insulin accordingly. I suspect that this is the case with Lichtenstein, but I also believe that, if he should visit our diabetic camp for girls, he would be impressed with the joyous natures of the campers and would find that they were being given prescribed diets not so very different from those served in their homes by the mothers of his own children; for his intelligent Swedish mothers undoubtedly found that restricted diets worked the best.

Statistics on Diabetes in Finland

The Vartiainens[51] estimated the number of diabetic patients in Finland and at the same time noted the variations in distribution according to age, sex and place of residence — urban or rural. They reached the conclusion that in 1942 the number of such patients was 5800, or 1.6 per 1000 of the total population, which is reported as 3,637,354. If this estimate were applied to the United States, it would mean less than 250,000 such patients. The Vartiainens' estimate is actually based largely on the number of persons receiving aid on account of diabetes, but it is rendered incomplete by the fact that a certain percentage of the inquiries remained unanswered, and by the fact that a large percentage of persons living in the country districts do not require aid of this sort. Without allowing for incomplete replies, chiefly in the urban districts, the Vartiainens reached an estimate of 2703 diabetic patients, but decided that a more nearly correct figure would be 2834. Adding to this number those whose occupations were on farms and in fisheries, they increased their estimate to the final one of 5800.

At the First University Medical Clinic in Helsinki the yearly number of cases treated varied widely, reaching a peak in the five-year period 1930–1935 and suffering a marked drop in the ensuing five years. They evaluated this variation as partly indicative of the interest of physicians or the preferential admission of patients to the hospital, because in the Second University Medical Clinic the figures were dissimilar.

Comparison of the diabetic mortality computed by insurance companies in Finland with the total mortality of the country gave the surprising result that the percentage of diabetic deaths remained practically constant at 1 per cent from 1890 to 1940, showing only an insignificant drop in the last five years of this period. Information from this source should probably be disregarded, since even in our country it is apparently not considered of great value.

The total diabetic mortality in Finland from 1927 to 1941 showed a steady increase. The number of deaths among males remained nearly stationary, but that among females nearly doubled, the deaths being confined chiefly to patients fifty years of age or above.

The estimated figure of 5800 diabetic patients in Finland, or 1.6 per 1000 population (1 patient among 667 persons), is far lower than the generally accepted incidence in the United States, which is at least 1 patient among 150 inhabitants. Perhaps the methods of computing mortality statistics in the two countries are different. It is said that in 1936 nearly 12 per cent of all deaths in Finland were ascribed to senility and an additional 2 per cent to unknown causes. Moreover, the mortality from tuberculosis was twenty-five times as high as that from diabetes. Some diabetic patients may have been in such groups and thus not included in the estimate.

Diabetic Associations, Societies, Foundations and Trusts

Compared with tuberculosis and cancer, diabetes is far behind in the support that it receives from associations, societies, foundations and trusts; yet the need for such support is manifest. There are certainly close to 1,000,000 living diabetic patients in the United States today. Diabetes ranks eighth in the causes of death, and in 1940 it was responsible for 1 death in every 40. Tuberculosis is decreasing, but diabetes is increasing, owing to the prolongation of life in the general population to the age at which the onset of diabetes is most frequent, and owing to the longer duration of life of such patients. One often speaks of childhood diabetes, forgetting that four or more times the life of the diabetic patient with onset in childhood will be lived as an adult.

Centers are needed for experimental investigation, the conducting of statistical studies and the stimulation of physicians in the surrounding communities. Emergency diabetic stations are needed in all large hospitals, hospitals must be properly equipped, and communities must be protected by an

extension of education in the treatment of the disease through hospital classes and outpatient departments. Above all, laboratory facilities must be extended to the practicing physician, because it is he who sees and treats most of the diabetic patients.

The Diabetic Association was inaugurated in London in 1934. The number of members has steadily grown to a total of 8400. Under the auspices of the association *The Diabetic Journal*, now in its fourth year, is issued every three months at the price of 1 shilling an issue. The Diabetic Association thus far is particularly a lay organization, conducted for the benefit of diabetic patients. During the war period it exerted much influence and was of great value to the country in bringing about the system of identification cards for diabetic patients, securing proper rations, making provision for such patients who were rendered homeless and helping to provide a home for diabetic children. It has issued a diabetic cookbook, presents occasional broadcasts on the radio, and is now interested in establishing a Banting Memorial Home. The honorary president is the noted author, H. G. Wells. The driving force among the medical profession has been Dr. R. D. Lawrence.

One of the earliest foundations for diabetes in the United States was the George S. Cox Medical Research Institute, established in 1931 at the University of Pennsylvania in Philadelphia. It is in the Hospital of the University of Pennsylvania, within the Department of Medicine. Dr. C. N. H. Long became the first director in 1932 and served until 1936. He was succeeded by Dr. F. D. W. Lukens, who has served from 1936 to the present time. The staff, in addition to its research work, conducts the outpatient section for diabetes of the Medical Clinic. The laboratory has contributed studies on the physiology and pathogenesis of diabetes. In the clinic, studies on immunity and of the value of exercise and other clinical observations have been made.

For eight years, — from 1934 through 1942, the children of the clinic were sent to the University Camps at Green Lane, where they were supervised by the staff with the assistance of specially trained medical students. This valuable activity was interrupted by the war but will be resumed as soon as possible.

The Renziehausen Foundation was opened on January 1, 1938, in the Children's Hospital of Pittsburgh. It was established through a gift from Miss Emily Renziehausen, of Pittsburgh, for the purpose of taking care of diabetic children. These patients are admitted without charge and are kept under continuous medical and educational supervision up to the age of sixteen. Connected with this foundation is a convalescent home at Large, Pennsylvania, to which children can be sent during the warmer months of the year. The staff of the foundation is made up of members of the faculty of the Medical School of the University of Pittsburgh and of nurses who are specially trained in pediatrics and diabetic work. Also, the Renziehausen Ward is used for the teaching of medical students and social-service workers. Both the children and parents are taught to know as much about diabetes as possible, and home conditions requiring improvement are usually corrected. Patients are accepted regardless of race, color, creed or financial status, up to the capacity of the foundation to give them proper care.

The New York Diabetes Association was established in New York City in 1934 through the efforts of Drs. Charles Bolduan and Herman O. Mosenthal, with the financial aid and the endorsement of Lucius Littauer. It was affiliated with the New York Tuberculosis and Health Association for three years, and then became independent, with offices at the New York Academy of Medicine. Drs. Herman O. Mosenthal, James Ralph Scott, Charles F. Bolduan, George E. Anderson and Frederick W. Williams have successively been presidents of the association.

The activities of the association have included the publication of *Fundamental Concepts*, which are pamphlets on various phases of diabetes. These have been widely distributed to the profession and to medical schools. A children's camp has been conducted since 1936. At first, the camp accommodated 30 children for a two-week period each. In the summer of 1945, 100 children were taken for a period of four weeks, each, and for 1946 a permanent site, with buildings accommodating approximately 250 children during the summer, has been acquired.

Research projects have been established during the last eight years, and numerous publications have resulted from them. Scientific meetings for physicians and lectures for the laity have been successfully carried out. The latest project of the New York Diabetes Association has been to found the Clinical Society of the New York Diabetes Association. This has secured a large membership among the physicians of Greater New York. This society holds meetings for physicians, is certifying specialists in diabetes in its area, and is taking steps for the standardization of diabetic clinics.

In Cincinnati in 1935, an organization for diabetes was begun. It was established under the name of the Council on Diabetes of the Public Health Foundation. It has led an active existence. Statistical studies have been made, public meetings have been held from time to time, and special posters and exhibits have been prepared and distributed. In 1939, a diabetes instruction service was inaugurated for the benefit of physicians who had the care of diabetic patients in the low income group. Refresher courses for nurses and physicians were established, and a radio program on diabetes was presented in a Sunday evening series. Letters sug-

gesting the possibility of employment of controlled diabetic patients were sent to the directors of industries. Diabetic identification cards were distributed, and a camp was operated for children. At one time an inventory of diabetes in the local schools was made, with the result that a sample survey of 5800 children disclosed only 3 diabetic children, thus indicating a number too small to warrant such an extension of the project to the entire school system.

The American Diabetes Association may be said to have been an outgrowth of the Cincinnati society. Dr. Cecil Striker, of Cincinnati, served as its first president and continues to be its efficient activating force. The first annual meeting was held in June, 1941, but the constitution of the association was adopted on June 12, 1940. Yearly meetings have been held, and the reports of the association's activities and papers read have been published. A notable contribution to the control of diabetes throughout the world has been the issuance of *Diabetes Abstracts*. This quarterly is published by the association and is financed with the help of the Eli Lilly Company. It contains abstracts of all articles on diabetes appearing in medical journals throughout the world. The membership of the association now exceeds 750.

The Philadelphia Metabolic Association was organized in 1934 by a group of physicians particularly interested in diabetes, composed mostly of the chiefs of various diabetic clinics in Philadelphia and their assistants. The association met monthly at different hospitals, at which time cases of interest were discussed. The association became interested in the broader aspect of the treatment of diabetes and admitted to membership social workers, nurses and dietitians whose chief interest was in this disease. It held several public meetings and organized and conducted for three years a summer camp for diabetic children. Lay interest in the diabetic problem increased steadily among public-spirited individuals, many of them outstanding citizens of Philadelphia who had diabetes. It was believed that more could be accomplished if the organization were incorporated, and this was done in 1940. At that time it was thought that the association could do a great deal more if the officers were lay people and the physicians acted in an advisory capacity.

The enlarged association conducted a much bigger camp for children during the summers of 1939, 1940 and 1941. The John B. Deaver Memorial Auxiliary became interested in the project and shared half its financing with the Philadelphia Metabolic Association. Children were admitted from clinics in Philadelphia, as well as some patients in the low-income group referred by private physicians. There were also patients from as far away as Maryland and New Jersey. These three camps had a completely adequate staff of a resident physician, two nurses, a technician and a dietitian, in addition to the usual camp personnel. Because of inability to obtain adequate personnel, the camps have been abandoned since the war.

The Association sponsored a series of newspaper articles on diabetes by a feature reporter. These articles discussed the disease and the rationale of its treatment and described the advantages to be expected from satisfactory diabetic control. They appeared each day for one week in the *Philadelphia Inquirer*, and it is believed that they did a great deal to increase lay knowledge concerning diabetes. The Association publishes quarterly the *Diabetic Digest*, which is somewhat similar to but smaller than the organ of the British association. This publication is written for the lay diabetic patient and is sent to all association members and other interested persons and groups. During the war the Association first began the distribution of identification cards to diabetic patients, and this work is continuing. An attempt was also made to improve the employment conditions of these patients.

The association at present has about 500 members, over 80 per cent of whom are diabetic patients, the remainder being physicians and other professional people.

The Diabetic Commission of the Pennsylvania Medical Society was organized ten years ago and is composed of a chairman, appointed by the president of the state society, and a representative of each councilor district in the society. In addition, under the commission's general guidance, each county society has a diabetic committee whose function it is to stimulate interest in diabetes and to see that a sufficient number of the society's meetings are devoted to this disease. Under the stimulus of the commission and its county chairmen, more than one hundred and thirty-five meetings of the county societies and their sub-branches were devoted to diabetes during 1942. The commission published the *Primer on Diabetes*, which was distributed to more than 3000 members of the state society and other interested persons. A second edition is being printed. The commission also prepared a motion picture on diabetes, which was suitable for lay groups, and this too had a wide circulation. During the war the commission supplied identification disks, as well as identification cards, to diabetic patients in the state. Under the auspices of a subcommittee in Philadelphia, a survey has been made of all death certificates on which the word "diabetes" appeared. The commission had an exhibit on diabetes at three meetings of the state society, and in conjunction with these concluded a series of talks, which were well attended.

The commission and the Philadelphia Metabolic Association are co-operating with the Philadelphia Tuberculosis Association in making a routine chest-plate examination of all diabetic patients in the city.

Diabetic organizations exist in Washington. The Diabetic Trust Fund of the State of Washington

was officially incorporated under the nonprofit corporation laws of the state in 1940, but had its actual beginning in 1924. In that year, $1000 was given to Dr. Lester J. Palmer to be used for the welfare of diabetic patients, and at my suggestion this money was employed to establish a small store at the Virginia Mason Hospital to dispense diabetic supplies. This store is still a valuable source of income for the fund. As funds accumulated, they were held in trust by the Virginia Mason Hospital until 1940, when the Diabetic Trust Fund was established as a separate organization. In 1945, the Fund represented about $30,000. Its growth is being aided by voluntary contributions, mostly small ones, by the net income of the diabetic store and by a modest annual spring drive, carried on each year chiefly for the purpose of financing the summer camps. The fund at present supports two projects — the publishing of *The Diabetic Monthly* and the financing of the summer camps.

The Washington Diabetes Association, a council of physicians interested in diabetes, was organized in May, 1942, but no further meetings were held because of the war. The next regular meeting is about to take place. About 300 diabetic patients have paid dues. The objectives of this body, as set forth in its constitution and bylaws, are similar to those of the American Diabetes Association. It is closely affiliated with the Diabetic Trust Fund.

Camp Banting for Diabetic Boys held its first session in the State of Washington, in 1938, and the Priscilla White Camp for diabetic girls in the same state in 1939. Annual sessions of two weeks each have since been held. These camps are conducted on the property of the Boy Scouts of America and the Camp Fire Girls. Plans are in progress to construct an independent camp building at these camps. Some children are taken free and others on part pay or full pay. The annual attendance at both camps averages 35 to 40 boys and girls.

For a good many years in Boston, a group of physicians from a dozen or more of the principal hospitals have met yearly and discussed problems of diabetic interest. No formal society has been established, but this subject is under consideration. The group has been sponsored to a considerable extent by the Massachusetts Tuberculosis League and has often had the advantage of the attendance of state or city officials from their respective departments of health.

A diabetic camp, established by physicians in Boston, has been in existence since 1927. It is the second one in the country, the first having been that of Dr. and Mrs. Wendt in Detroit. Fortunately, during the last fourteen years the Association of Universalist Women has placed at the camp's disposal the grounds and buildings of the Clara Barton Homestead in North Oxford, Massachusetts. In addition, the members of this body have materially enlarged and improved the equipment each year. In the last twelve months, the Clara Barton Homestead Camp accommodated four sets of diabetic girls in groups of 50, each group being taken for a two-week period. Many of these children remained for more than two weeks, however, so that actually only 123 children had the benefit of the camp. Its total expense was approximately $10,000, of which the children voluntarily contributed about half. Each year diabetic girls are offered an opportunity to go to the camp, and preference is given to those who can make no payments or only small, voluntary ones. The balance of the expense has been largely borne by the Association of Universalist Women, the friends of physicians of the George F. Baker Clinic of the New England Deaconess Hospital, and the Diabetic Fund.

The Diabetic Fund was inaugurated at the Boston Safe Deposit and Trust Company on February 2, 1944. It was established in this trust company because of its particular interest in the Charity Fund and its experience with it. Sums given to the Diabetic Fund are held in trust by the trust company, and the income or a limited part of the principal is available for promotion of diabetic research and diabetic activities under the supervision of an advisory committee. This committee consists of a representative appointed every seven years by the dean of the Tufts College Medical School, one similarly appointed by the dean of the Harvard Medical School and five others associated with the George F. Baker Clinic of the New England Deaconess Hospital. This endowment has grown, and by November 21, 1945, it had received $93,102.18 in gifts and pledges and had disbursed $15,000. A friend of the undertaking, desiring that only the income of his donation should be used, established along the same lines, with the same advisory committee, the Horace E. Munroe Permanent Diabetic Fund as a component of the Permanent Diabetic Fund, and these permanent funds have together reached $7877. Thus far grants have been made, particularly because of the expressed wish of the donors, for research in alloxan and diabetic pregnancies. In addition, allotments have been made for children in diabetic camps and for a grant to the American Diabetes Association.

Finally, a special endeavor has been made in connection with the present building-fund campaign at the New England Deaconess Hospital to secure funds for 50 new diabetic beds and other diabetic projects, among which is a coma unit. Gifts have been sought from a multitude of patients, with the idea that $1 received from 1000 different patients would accomplish far more than $1000 from one, because in the former case there would be driven home to many patients the need for research and improvement in the care of such patients, and incidentally make them realize the desirability of animal experimentation. Patients and friends of the New England Deaconess Hospital have re-

sponded generously to solicitation, and at the present moment $243,000 has been received from 3112 persons for extension of the facilities of the hospital along diabetic lines. It seems particularly desirable that this plan of securing gifts from the many and not from the few should be cultivated, and it is the hope of those inaugurating the diabetic funds at the Boston Safe Deposit and Trust Company and the diabetic projects at the New England Deaconess Hospital that the example set will be followed in other localities.

It is a sign of the increasing interest in and importance of diabetes that in the plans for the addition to the Rhode Island Hospital in Providence $54,000 has been set aside for the Diabetes Clinic.

Active work in diabetes is in progress in a multitude of hospitals and laboratories. I hesitate to publish the above list of societies, but do so partly with the idea that this will lead to corrections and amplifications, which I shall receive with gratitude. At the Mayo Clinic, in St. Louis, in Omaha, Nebraska, at the University of California and in various hospitals in Chicago extremely active diabetic investigation is going on. Diabetic camps have been conducted at various times in connection with work in the above localities, and continuously at the University of California since 1938. I understand that a diabetic trust fund is in process of creation in Portland, Oregon, and that an organization of somewhat wider scope is being formed in Omaha.

References

49. Lichtenstein, A. *Treatment of Children's Diabetes: Ten years' experience without dietetic restrictions.* Chapter in *Opera Paediatrica.* Edited by Jundell, I., Lichtenstein, A., and Wallgren, A. Uppsala: Almquist & Wiksells, 1945. Pp. 370-391.
50. Joslin, E. P., Root, H. F., White, P., and Marble, A. *The Treatment of Diabetes Mellitus.* Seventh edition. 783 pp. Philadelphia: Lea & Febiger, 1940. P. 687.
51. Vartiainen, I., and Vartiainen, O. Studien über den Diabetes mellitus in Finnland. III. Das Vorkommen des Diabetes. *Acta med. Scandinav.* **119**:364-379, 1944.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 32141

PRESENTATION OF CASE

A sixty-year-old housewife was admitted to the hospital because of jaundice.

A year and a half before admission the patient became weak and lethargic and had mild anorexia. She remained in bed for several weeks and slowly regained strength until four months before admission, when she became insidiously tired and was noted to have jaundice. Her skin itched slightly, and her urine became dark. Her appetite disappeared. At the height of the jaundice a Graham–Cole test was unsuccessfully attempted by her physician. On a low-fat, low-calorie diet the jaundice slowly disappeared, but it recurred one month before admission. At that time she had two episodes a week apart of sudden acute colicky pain in the right upper quadrant. Each attack lasted half an hour and was not associated with nausea or vomiting. She had had no chills or fever at any time. During that month she was given iron and liver for anemia. The iron was stopped four days prior to admission, and after that her stools were clay colored. The color of the stools had not been observed previously. There had been a 25-pound weight loss in the four months prior to admission. There had been no swelling of the abdomen or ankles at any time.

The patient had been jaundiced as a child. Seven years before admission an appendectomy had been performed. Prior to the onset of jaundice it was routine for the patient to have one or two cocktails before lunch and dinner and a highball at bedtime. Thereafter her appetite for alcohol decreased proportionately with her desire for food so that she had only an occasional cocktail at noon.

On physical examination the patient was thin and sallow, with a yellowish-brown skin and yellow scleras. There were Grade I apical and aortic systolic murmurs. The liver was palpable in the right hypochondrium and in the epigastrium; the edge was tender and round and the surface was questionably nodular. The tip of the spleen was palpable. There was a firm round mass in the right upper quadrant, immediately beneath the liver edge.

The temperature was 98.6°F., the pulse 75, and the respirations 20. The blood pressure was 132 systolic, 76 diastolic.

The hemoglobin was 12.8 gm. The white-cell count was 8800, with 59 per cent neutrophils, 28 per cent lymphocytes, 7 per cent monocytes and 6 per cent eosinophils. The urine had a specific gravity of 1.028 and gave a ++ test for albumin and a +++ test for bile. The sediment contained 25 white cells and 10 epithelial cells per high-power field. The test for urobilinogen was positive in a dilution of 1:100. The prothrombin time was 30 seconds (normal, 18 seconds), and the serum protein 6.7 gm., with an albumin globulin ratio of 2:1.

The nonprotein nitrogen was 29 mg. per 100 cc., and the alkaline phosphatase 26.7 Bodansky units. The stools varied from brown to clay colored and from strongly to slightly positive for bile; they were guaiac negative. During the Graham test the gall bladder contained poorly concentrated dye and was not well visualized; it appeared to contract after a fat-containing meal. No stones were seen. Fluoroscopically the stomach contained a questionable filling defect close to the cardia in the lesser curvature. The stomach was long and low in position. The second portion of the duodenum lay considerably more to the right than usual, and there was a suggestion of a filling defect at the junction of the second and third portions. So far as could be demonstrated the duodenal loop and head of the pancreas were readily movable. At the end of six hours the barium was scattered through the terminal ileum and colon.

On the sixth hospital day the patient had an attack of biliary colic and the jaundice increased.

An operation was performed on the eighth hospital day.

Differential Diagnosis

Dr. Wyman Richardson: This is a case of jaundice, and it presents the same old problem of deciding whether it was intrahepatic or obstructive, or both. Let us briefly review the clinical history for a moment. I have no answer for the lethargy and weakness, which were present one and a half years before entry, as part of the present illness. It makes some difference regarding the ultimate diagnosis. The skin itched slightly at the time of admission, and the urine became dark. Although it says "slightly," that may be of some importance, and as you know it suggests biliary obstruction rather than intrahepatic jaundice. At the height of the jaundice the Graham–Cole test was unsatisfactory. I believe that it is usually considered rather pointless to try to visualize the gall bladder by x-ray in the presence of deep jaundice. Is that so, Dr. Lingley?

Dr. James R. Lingley: Yes.

Dr. Richardson: The low-fat diet was all right in the presence of jaundice, but I should say that a high-protein, high-carbohydrate, high-calorie diet containing numerous supplementary vitamins was indicated rather than a low-calorie diet. The pain is described as colicky, but it appeared to be of brief duration.

I "saw red" when I read that both iron and liver were given for anemia. This is done frequently, but if the anemia improves, one does not know whether the improvement was due to the giving of liver or to the giving of iron. It is rare that both iron and liver need to be given to the same patient.

"The patient had been jaundiced as a child." I take it that that means an episode of jaundice and not prolonged jaundice throughout childhood. It could be interpreted as infectious hepatitis, and one may consider that a previous attack of infectious hepatitis may predispose the liver to damage later on. There is some evidence of this fact in a paper published by Dr. Altschule and Dr. Gilligan.* To me the evidence is not entirely convincing, since it is based on certain tests some of which, it seems to me, are not entirely specific for liver failure.

There is a slight alcoholic aroma to the history. That may be put in to make it difficult to decide about the question of the cause of this jaundice.

The patient had a yellow-brown skin. I do not know the nationality.

Dr. Tracy B. Mallory: She was Irish.

Dr. Richardson: The yellow-brown skin is suggestive of biliary obstruction rather than intrahepatic jaundice.

The "questionably nodular" liver leaves me cold. I think that it is extremely difficult to feel a nodular liver through an abdominal wall. One may feel a grossly nodular liver, such as occurs in the hepar lobatum of syphilis, and with especially big tumor nodules one may get the impression that the liver is irregular, but, as I have said, a questionably nodular liver means nothing to me.

The fact that the tip of the spleen was palpable is of great importance, and if that notation appears on the record one can usually accept it. In other words a positive finding seems to me more important than a negative finding, especially regarding the spleen.

The firm round mass in the upper quadrant could well have been a dilated gall bladder, although it is frequently difficult to feel a gall bladder and sometimes it does not give the impression of being firm.

The 12.8 gm. of hemoglobin indicates a slight anemia. It is perhaps a definite one, even though this patient was a woman. The blood differential was normal. I shall assume that the 6 per cent eosinophils was within the normal limits. The urine was essentially normal, except for the fact that bilirubin was being passed through the kidney. There were a few white cells, but I do not believe that they were significant.

Urobilinogen was present in the urine in a dilution of 1:100. That is definitely increased and means, according to my own definition, that bilirubin was excreted into the gut, because as I understand it, urobilinogen is formed from bilirubin only in the gut; it is reabsorbed and excreted normally through the kidney to some degree, but it may be excreted in increased amounts when there is an increased load of bilirubin going through the biliary system. It may also be increased in some cases when there is inability on the part of the liver to excrete urobilinogen, whereas at the same time the liver can excrete bilirubin. That is confusing. The point is that the presence of increased uro-

*Altschule, M. D., and Gilligan, D. R. Chronic latent hepatitis following catarrhal jaundice. *New Eng. J. Med.* 231:315-317, 1944.

bilinogen in the urine should be a great help, but it frequently is not. In this case it is corroborative evidence that bilirubin was being excreted through the biliary tract into the gut.

The prothrombin time was slightly elevated, and the serum protein was normal. The normal albumin-globulin ratio suggests that there was no considerable degree of intrahepatic disease. The alkaline phosphatase was distinctly elevated, which is in favor of biliary obstruction and somewhat in favor of neoplastic disease.

I want to ask Dr. Lingley whether the head of the pancreas ever is movable. I had not supposed that it was.

DR. LINGLEY: I should not expect it to be.

DR. RICHARDSON: I wonder why it said "readily movable."

DR. LINGLEY: I believe that it is a mistake that the examiner meant the duodenum, rather than the pancreas.

DR. RICHARDSON: Is there or is there not a peptic ulcer in the midportion of the duodenum? The report is mildly suggestive. Would you interpret that as being questionable?

DR. LINGLEY: Yes. The second portion of the duodenum is sometimes difficult to examine because you cannot fill it completely. Small lesions may be hard to demonstrate and in this case I judge that there was some question about it in the examiner's mind.

DR. RICHARDSON: Is there any other comment that you would like to make?

DR. LINGLEY: In regard to the gastric filling defect, the left lobe of the liver can push over against the stomach immediately beneath the cardia and produce a pressure defect where this one is described.

DR. RICHARDSON: I think that the evidence is strong that this patient had a biliary obstructive lesion. The question is, Was it a ball-valve effect or was there a partial obstruction that allowed a certain amount of bile to get through but not the normal amount? Can we rule out intrahepatic disease? I do not believe that one can completely rule it out, but it seems to me that the clinical history is opposed to it, except for the use of alcohol. There was no edema, ascites or varices, and the serum protein was normal. The prothrombin time can be elevated in either condition. There is no note whether the prothrombin time returned to normal after the administration of vitamin K_1. If it did, it might be of some value in indicating that this was an obstructive lesion.

What type of lesion was it? I think that in the wards we frequently have a grand guessing match and end up by operating on the patient to find out. I sincerely believe that any patient with biliary obstruction should be operated on, even though the probability of a malignant tumor may be strong. I remember one patient who was not operated on and whom Dr. Mallory finally examined, only to find a miserable little stone in the mouth of the common bile duct. As between obstruction, tumor and stone, in favor of tumor are the enlarged gall bladder, the considerable increase in the alkaline phosphatase and the appreciable weight loss. In favor of stone is the history of colicky pain, which I think may occur with either condition but is nevertheless suggestive of stone. We are told that in the presence of stone the gall bladder is usually small and not large. The palpable spleen is not much more in favor of stone than it is of malignancy, but it is suggestive of intrahepatic disease.

Finally, should one consider the possibility of a peptic ulcer in the region of the ampulla, which had caused constriction and resulted in an obstructive lesion? That does occur rarely, but I should expect it to occur in a chronic, long-standing ulcer, of which there is a little evidence in this patient.

I cannot think of any other way to narrow this down. I think that this patient had a malignant tumor, probably arising in the pancreas. It is possible that she had both some type of obstructive lesion and intrahepatic disease, but I am not going to complicate matters by saying that. I will say that there was no intrahepatic disease other than that associated with biliary obstruction, a beginning biliary cirrhosis, if you will. I believe that it is more usual to have intermittent jaundice with stone than with tumor, although I think that it does occur with the latter. My final diagnosis is, as I have said, malignant tumor, probably carcinoma of the head of the pancreas.

CLINICAL DIAGNOSIS

Carcinoma of head of pancreas.

DR. RICHARDSON'S DIAGNOSIS

Malignant tumor, probably carcinoma, of head of pancreas.

ANATOMICAL DIAGNOSIS

Carcinoma of ampulla of Vater.

PATHOLOGICAL DISCUSSION

DR. MALLORY: I am sorry that Dr. Chester M. Jones was called away. I had hoped that he would discuss this case. He thought, as Dr. Richardson did, that the probable diagnosis was carcinoma of the head of the pancreas and that the patient deserved exploration. This was carried out and the enlarged gall bladder contained rather light colored bile and quite a bit of gravel-like sediment. The common duct was dilated. An attempt to pass a probe through the ampulla was fruitless, and the surgeon had the impression that with the tip of the probe he could feel a soft tumor mass rather than a stone. Since he was unable to decide from above, he opened the duodenum in order to palpate the ampulla from both sides. On doing that he became convinced that there was a tumor in the ampulla.

He could not make out any extension, and it seemed that it might be possible to resect it. It was not believed, however, that the patient could stand the operation at that time. So the gall bladder was drained and the patient was sent home for a few weeks, to return to the hospital for radical resection. At that time the pyloric antrum of the stomach, the first and second portions of the duodenum and half of the pancreas were resected. The remaining pancreas was sutured into the intestinal wall, and the operative reconstructions were carried out. After a stormy convalescence she was able to leave the hospital in fairly good shape.

The resected specimen showed a small tumor — only about 2 cm. in diameter — sharply restricted to the region of the ampulla but extending a little way up the common bile duct and a little way up the pancreatic duct. The mouths of both the bile duct and the pancreatic duct were found in the small ulcerated crater of the tumor. Microscopic examination showed a fairly well differentiated adenocarcinoma. There were numerous enlarged regional lymph nodes, but all of them were free from metastases, and so far as one could judge, the tumor seemed to have been completely removed.

DR. RICHARDSON: Did they biopsy the liver?

DR. MALLORY: No biopsy specimen was taken. The liver was smooth and moderately bile stained. They thought that it was normal except for the bile stasis, and at the time of the second operation most of that had disappeared.

A PHYSICIAN: Where did you say that the tumor arose?

DR. MALLORY: It was a carcinoma of the ampulla of Vater. There are both benign papillomas and malignant carcinomas of the ampulla. I am not sure that in this hospital we have ever seen a benign papilloma, but there are numerous cases on record. One other point worth remembering when the question of operation arises is that it is quite possible to find a benign as well as a malignant neoplastic obstruction; if the patient can be suitably prepared for operation, it is well worth the risk to attempt resection.

CASE 32142

PRESENTATION OF CASE

First admission. A thirty-four-year-old Irishman entered the hospital because of severe pain in the epigastrium and left flank of four days' duration.

Five years before entry he first began to suffer from gnawing, burning nonradiating pain in the epigastrium following meals by one or two hours and usually relieved by food or sodium bicarbonate. These attacks had been cyclic in nature, with two-month to three-month periods of postprandial pain alternating with four-month to five-month periods of freedom from symptoms. Prior to entry he had had severe postprandial epigastric distress for three weeks, gradually becoming worse and only partially relieved by food and alkali. On two occasions he vomited recently ingested food without gross blood. In addition to the epigastric distress he developed pain in the left groin that radiated to the flank and back.

Physical examination was negative except for a soft apical systolic murmur. The blood pressure was 140 systolic, 85 diastolic. The laboratory studies were essentially negative. A barium meal disclosed a constantly irregular duodenal cap with a fleck of barium in its lower portion.

After three weeks in the hospital the patient was discharged to be followed in the Out Patient Department.

Second admission (thirteen years later). During the interval the patient continued to have epigastric pain but refused to follow the dietary regimen described. He was, however, able to continue his work. The morning of re-admission he left home for work feeling well, but suddenly he was doubled up by an excruciating midline stabbing abdominal pain that spread to the umbilicus. This pain remained constant.

On physical examination the patient was a well developed and well nourished pale perspiring man in acute abdominal distress. The neck and chest were negative. The abdomen was tense with generalized spasm, most marked in the epigastrium. There was generalized tenderness; peristalsis was absent.

The temperature was 99°F., the pulse 112, and the respirations 40. The blood pressure was 170 systolic, 90 diastolic.

The white-cell count was 14,000, with 87 per cent neutrophils. The urine was normal.

The patient was taken to the operating room, and abdominal exploration was done. The duodenum was found to be heavily scarred, and there was a perforated duodenal ulcer, which was closed by sutures.

After the operation the patient was improved but continued to have epigastric pain and to run a temperature of 100°F. Two days later his condition suddenly became worse. He complained of severe, constant epigastric pain that occasionally radiated into the right groin. There was no vomiting. Morphine failed to bring relief. The blood pressure was 150 systolic, 90 diastolic. The abdomen was board-like, with tenderness and rebound pain; peristalsis was absent. He was prepared for operation, but after induction of anesthesia, his color suddenly became poor, his respirations shallow, and his pulse imperceptible. Despite all resuscitatory measures the patient went downhill rapidly and died.

DIFFERENTIAL DIAGNOSIS

DR. HOWARD ULFELDER: This patient, in brief, was a man of forty-seven with duodenal ulcer of

eighteen years' standing. No other organic lesion is described, nor does the history suggest that any was suspected.

The last admission was precipitated by perforation into the free peritoneal cavity. This was treated in orthodox surgical fashion, but the immediate postoperative course was marred by persistent fever and epigastric pain. On the second day there was a sharp turn for the worse. This complication was obviously considered amenable to surgical correction, but with the induction of anesthesia the patient took another sharp downward turn and soon expired.

Could this have been a pure anesthetic death? If so, one must still speculate on the nature of the complication that necessitated return to the operating room. It appears more plausible to me to assume that the burden of anesthesia alone was more than this patient could stand; his compensatory mechanisms had already been called on, and his reserves were spent. This view is supported by the fact that anesthesia precipitated a state of profound circulatory collapse. Although the possibility of asphyxia secondary to laryngospasm or aspirated gastric contents should be mentioned, the account of this man's terminal moments does not fit this diagnosis.

Turning now to the mishap that occurred on the second postoperative day, one can suspect that it was due either to a vascular accident or to peritonitis. The past history gives me no leads, although there is mention of pain in the left groin and flank at the time of the first hospital admission and in the right groin on the day of death. The former I shall ascribe to an unusual but not unheard of radiation from the upper gastrointestinal tract. The latter is easily explained by the presence of irritating or infected fluid in the right gutter.

Among vascular accidents, only mesenteric thrombosis deserves attention. Some evidence of obstruction usually accompanies this lesion. None is described here. Coronary occlusion, dissecting aneurysm and pulmonary embolism fail to fit either the symptoms or the physical findings.

Under the heading of peritonitis, mention must be made of a perforated gall bladder, appendix and bowel and of acute pancreatitis. None of these can be completely excluded, but all appear extremely unlikely.

Three lesions remain for serious consideration. Leakage at the site of the recent duodenal suture appears the likeliest, but according to the literature this is extremely rare. Rupture of a previously localized abscess would not be expected so soon after the primary insult. My diagnosis is perforation of a separate peptic ulcer. This also is infrequent, but ulcers are notoriously multiple during periods of activity and one example of this coincidence was noted in a review of 334 cases of benign perforated ulcer observed in this hospital.*

I predict, therefore, that post-mortem examination revealed early generalized peritonitis, recent duodenal perforation with intact closure, and a separate ulcer (probably gastric), with perforation into the free peritoneal cavity.

DR. RODOLFO E. HERRERA: When the patient was taken to the operating room the second time, it was our feeling that we were compelled to rule out a leak from the site of the previous perforation or from a new site. Although the patient had complained of pain almost constantly after recovery from his first anesthesia, his condition appeared good; there was, however, a definite exacerbation of pain on the second postoperative day. At that time an abdominal tap yielded coffee-grounds material grossly identical to that obtained through the Levine tube.

CLINICAL DIAGNOSIS

Perforated gastric ulcer.

DR. ULFELDER'S DIAGNOSES

Duodenal ulcer, repaired.
Perforated gastric ulcer.
Generalized peritonitis.

ANATOMICAL DIAGNOSIS

Multiple perforated peptic ulcers of duodenum.

PATHOLOGICAL DISCUSSION

DR. HERRERA: At the time of the second laparotomy the ulcer on the anterior duodenal wall was found to be closed over adequately by an omental tab. On the posterior wall, just proximal to the pylorus, a second perforation was found; this measured at least 7 mm. in diameter, and through it gastric contents poured out freely. At that point in the operation the patient was no longer breathing and his heart had stopped. We found it impossible to tell how old the second perforation was; in other words, we were not certain whether this man had perforated the second ulcer on the second postoperative day or whether two perforations had been present at the time of the first operation.

DR. TRACY B. MALLORY: Dr. Herrera's description of the findings at the second operation appears to explain adequately the terminal episode. Permission for post-mortem examination was refused.

*Ulfelder, H., and Allen, A. W. Acute perforation of ulcers of stomach and duodenum. *New Eng. J. Med.* 227:780-784, 1942.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. John Fallon, M.D.

Official Organ of
The Massachusetts Medical Society
and
The New Hampshire Medical Society

Editorial Board

Joseph Garland, M.D. A. Warren Stearns, M.D.
Shields Warren, M.D. Chester S. Keefer, M.D.
C. Guy Lane, M.D. Fletcher H. Colby, M.D.
William A. Rogers, M.D. Robert L. Goodale, M.D.
Henry R. Viets, M.D. Chester M. Jones, M.D.
Robert M. Green, M.D. Harvey R. Morrison, M.D.
Charles C. Lund, M.D. Maxwell Finland, M.D.

Associate Editors

Thomas H. Lanman, M.D. Donald Munro, M.D.
Henry Jackson, Jr., M.D.

Walter P. Bowers, M.D., Editor Emeritus
Robert N. Nye, M.D., Managing Editor
Clara D. Davies, Assistant Editor

Subscription Terms: $6.00 per year in advance, postage paid, for the United States (medical students, $3.50 per year); Canada, $7.04 per year (Boston funds); $8.52 per year for all foreign countries belonging to the Postal Union.

Material should be received not later than noon on Thursday, two weeks before date of publication.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

PEDIATRIC SURVEY

Complacence is the natural enemy of progress but, fortunately, satisfaction with any level of achievement, if too long indulged, is usually shattered by forces from without, coming to demand a higher grade of production in favor of the consumer. Medicine in this country has not ordinarily needed such stimulation for it has felt the necessity of meeting new challenges, and pediatrics, no less than other branches of medicine, has so far always found ahead of it new standards on which to form its line.

Pediatrics, spurred on perhaps by political rumblings that suggest a storm on the horizon, has now initiated its own psychoanalytical survey, with the American Academy of Pediatrics in the role of analyst; it has found wisdom in the Socratic injunction to know thyself.

This study of child-health services has already been conducted during the past year in North Carolina as a pilot state, and similar country-wide state programs are about to be launched. A steering committee has been appointed within the American Academy of Pediatrics representing the Academy, the American Pediatric Society and the Medical Advisory Board of the Children's Bureau. Dr. John P. Hubbard, of Boston, has accepted the position as director of the study.

The inquiries to be made will cover four major fields: pediatric education; distribution, qualification and activities of professional personnel; hospital and clinic facilities, and general health services. The study in Massachusetts, soon to be initiated, will be directed by Dr. Lendon Snedeker, of Boston; it has been approved by the Council of the Massachusetts Medical Society.

The work of gathering data will fall on the pediatricians of the state who will be asked to fill out questionnaires concerning their own activities and assist in obtaining information from physicians in private practice and from hospitals. They will also be asked to help publicize the program through newspapers, radio broadcasts and group meetings.

Such a program suggests that the pediatricians of the country intend to do a thorough job in finding out what type of care is being given to our children by hospitals, health services, the general practitioners and themselves. It is hoped that the study will determine, so far as possible, what quality as well as what type of service is delivered, in what proportions pediatric practice is conducted for the benefit of the patient and of the doctor, and what the true standards of service should be.

The evaluation of present methods of child care and the establishment, where necessary, of better ones are undertakings that warrant general support.

DANGERS OF CHEMOPROPHYLAXIS

In the past few years, a number of papers have appeared indicating that prolonged and continuous administration of sulfanilamide or sulfadiazine in small doses may be used effectively as a prophy-

lactic against hemolytic streptococcus infections. At first, the writers were concerned primarily with the prevention of recrudescences of rheumatic fever, and the data that they present suggest that such recrudescences were significantly reduced in susceptible individuals, as compared with controls in whom such prophylaxis was not used. Some subjects had to be eliminated from the treated groups because of toxic reactions, which sometimes were quite serious. The types of patients chosen, however, were such that considerable risks were warranted since hemolytic streptococcus infections in them would frequently have been followed by serious rheumatic activity resulting in crippling and even fatal cardiac involvement.[1–5]

It is interesting that positive throat cultures for hemolytic streptococci were not eliminated or prevented and that their incidences were not appreciably reduced among the recipients of this form of prophylaxis. Furthermore, in studies on cases of hemolytic streptococcus tonsillitis and pharyngitis in which therapeutic doses of sulfadiazine had been used, the incidence of Group A hemolytic streptococci in throat cultures was found to be reduced only during the period of treatment; after treatment was stopped, positive cultures were found just as frequently in patients who had been treated with the full doses continuously for three to seven days as they were in comparable untreated cases.[6–9]

The possibility of developing sulfonamide-resistant strains of pathogenic organisms during treatment with doses of drug that are ineffective for the complete elimination of the infecting organism is a serious and important consideration in the prophylactic use of chemotherapeutic and antibiotic agents. In vitro and in experimental infections in animals such resistance can be readily produced in many organisms by prolonged exposure to subeffective concentrations of these therapeutic agents. Whether this is a process of selection whereby the resistant variants survive or whether it is due to a change in the metabolism of the organism — a sort of acclimatization — is not entirely clear. It is evident, however, that the less susceptible the organism is in the first place, the easier it is to enhance its resistance. Furthermore, it is reasonable to suppose that the extensive and prolonged use of drugs in subeffective amounts carries with it the greatest danger of the development and spread of resistant strains, irrespective of the mechanism whereby the organisms become resistant. Attention has been called in these columns on previous occasions both to the dangers of the continuous use of sulfonamides to the patient[10] and to the possibility of the development and spread of resistant strains.[11] These dangers and the responsibilities of the physician and patient with respect to sulfonamide prophylaxis and treatment have been ably reviewed by Morgan and Turner.[12]

Two types of mass prophylaxis with sulfadiazine have been employed in military establishments. One of these was a brief course, varying from a single dose to several doses given over a period of one or two days, for the purpose of preventing and eliminating meningococcal infections.[13–15] The other was a continuous administration of small doses of sulfadiazine over several weeks, given primarily for the purpose of preventing hemolytic streptococcus diseases.[16–18] The former resulted in immediate and almost complete elimination both of infections and of carriers until the organisms were gradually introduced again from outside. The latter produced a reduction in manifest streptococcal diseases without eliminating the organisms from carriers or preventing their spread. These results could have been anticipated from the extreme sensitivity of the meningococcus to sulfadiazine on the one hand and the resistance of the hemolytic streptococci on the other. Resistance or fastness of meningococci to sulfadiazine is produced with the greatest difficulty even in vitro, whereas it is readily produced in streptococci. Other factors concerned with the host-parasite relation may also be of equal or greater importance with respect to these two organisms, but they are difficult to evaluate. At any rate, the anticipated effect of the continued use of sulfadiazine in small doses in a population heavily infected with virulent streptococci finally materialized. Resistant strains of hemolytic streptococci spread throughout several of the units where sulfadiazine prophylaxis was being carried out. These resistant strains essentially replaced susceptible strains and gave rise to rather extensive outbreaks of hemolytic streptococcus infections.

Two reports of such a sequence of events in different Navy training stations have recently been reported,[19, 20] and others have undoubtedly occurred. It is difficult to tell without a considerably greater amount of information than has been made available thus far whether the widespread prophylactic program adopted by the Navy had the total effect on the training program that was anticipated by the medical authorities. Data, likewise, are lacking from which one can estimate just how much harm was done in misdiagnosed or improperly treated cases as a result of sensitization or from other toxic effects that resulted directly or indirectly from this prophylactic regime. It is clear from these experiences, however, that sulfonamide prophylaxis on a large scale and over a long period carries with it considerable possibilities of harm, which must always be weighed against the anticipated benefits.

No doubt the availability of penicillin in large quantities, particularly in the form of troches and oral preparations, has suggested to many physicians the possibility of its continuous use in the prophylaxis of various types of infections. Although fewer and perhaps less serious toxic effects may be expected from penicillin than from the sulfonamides, the possibilities for harm should be explored under rigidly controlled conditions before any such programs are undertaken.

References

1. Coburn, A. F., and Moore, L. V. Follow-up report on rheumatic subjects treated with sulfanilamide. *J. A. M. A.* **117**:176, 1941.
2. Thomas, C. B. Prophylactic treatment of rheumatic fever by sulfanilamide. *Bull. New York Acad. Med.* **18**:508-526, 1942.
3. Kuttner, A. G., and Reyersbach, G. Prevention of streptococcal upper respiratory infections and rheumatic recurrences in rheumatic children by prophylactic use of sulfanilamide. *J. Clin. Investigation* **22**:77-85, 1943.
4. Feldt, R. H. Sulfanilamide as prophylactic measure in recurrent rheumatic infection: controlled study involving 131 "patient-seasons." *Am. J. M. Sc.* **207**:483-488, 1944.
5. Slocumb, C. H., and Polley, H. F. Prophylactic use of sulfonamide compounds in treatment of rheumatic fever. *M. Clin. North America* **28**:838-843, 1944.
6. Plummer, N., Duerschner, D. R., Warren, H. D., Rogliano, F. T., and Sloan, R. A. Penicillin therapy in hemolytic streptococcic pharyngitis and tonsillitis. *J. A. M. A.* **127**:369-374, 1945.
7. Commission on Acute Respiratory Diseases. Study of food-borne epidemic of tonsillitis and pharyngitis due to beta-hemolytic streptococcus, Type 5. *Bull. Johns Hopkins Hosp.* **77**:143-210, 1945.
8. Rubenstein, A. D., and Foley, G. E. Effect of chemotherapy on duration of carrier state following scarlet fever. *New Eng. J. Med.* **233**:315-322, 1945.
9. Meads, M., Flipse, M. E., Jr., Barnes, M. W., and Finland, M. Penicillin treatment of scarlet fever; bacteriological study of nose and throat of patients treated, intramuscularly or by spray, with penicillin and comparison with sulfadiazine. *J. A. M. A.* **129**: 785-789, 1945.
10. Editorial. Dangers of continuous sulfonamide therapy. *New Eng. J. Med.* **230**:365, 1944.
11. Editorial. Prophylactic use of sulfonamides. *New Eng. J. Med.* **231**: 857-859, 1944.
12. Morgan, H. J., and Turner, R. H. Chemoprophylaxis of streptococcus disease. *Bull. New York Acad. Med.* **21**:37-43, 1945.
13. Kuhns, D. M., Nelson, C. T., Feldman, H. A., and Kuhn, L. R. Prophylactic value of sulfadiazine in control of meningococcic meningitis. *J. A. M. A.* **123**:335-339, 1943.
14. Pilot, I. Sensitiveness of meningococci to sulfonamides: rapid effect of administration of two grams of sulfadiazine on carriers of Neisseria intracellularis (meningococcus). *J. A. M. A.* **127**:310, 1945.
15. Schoenbach, E. B., and Phair, J. J. Dissemination and control of meningococcal infections. *J. Mt. Sinai Hosp.* **12**:624-636, 1945.
16. Holbrook, W. P. Army Air Forces rheumatic fever control program. *J. A. M. A.* **126**:84-87, 1944.
17. Coburn, A. F. Prevention of respiratory tract bacterial infections by sulfadiazine prophylaxis in United States Navy. *J. A. M. A.* **126**:88-93, 1944.
18. Hodges, R. G. Use of sulfadiazine as prophylactic against respiratory disease. *New Eng. J. Med.* **231**:817-820, 1944.
19. Sulfadiazine resistant strains of beta hemolytic streptococci; appearance during course of sulfadiazine prophylaxis at large naval training center. Epidemiology Unit Number 22. *J. A. M. A.* **129**: 921-927, 1945.
20. Damrosch, D. S. Chemoprophylaxis and sulfonamide resistant streptococci. *J. A. M. A.* **130**:124-128, 1946.

MASSACHUSETTS MEDICAL SOCIETY

REVIEW LECTURE COURSE

The following is a detailed program of the balance of the Review Lecture Course, which concludes on May 15.

APRIL 17. ALLERGY. *Chairmen*: John L. Fromer and Francis M. Rackemann.

3:00–4:45. Round-Table Discussion on Hay Fever and Asthma. Walter Burrage: assistant physician, Massachusetts General Hospital. Calvin B. Faunce: consulting surgeon, Massachusetts Eye and Ear Infirmary. John L. Fromer: director, Department of Allergy and Dermatology, Lahey Clinic. J. Evarts Greene: assistant in medicine, Massachusetts General Hospital. Sanford B. Hooker: professor of immunology, Boston University School of Medicine. Francis M. Rackemann: lecturer in medicine, Harvard Medical School; physician, Massachusetts General Hospital. Leroy E. Schall: professor of laryngology, Harvard Medical School; chief, Department of Otolaryngology, Massachusetts Eye and Ear Infirmary.

NOSE AND THROAT DISEASES. *Chairmen*: Calvin B. Faunce and Leroy E. Schall.

4:45–5:30. DEAFNESS AND WHAT CAN BE DONE ABOUT IT. Moses H. Lurie: assistant professor of otology, Harvard Medical School; surgeon in otolaryngology, Massachusetts Eye and Ear Infirmary; consulting otolaryngologist, Massachusetts General Hospital.

5:30–6:00. Emergencies Involving the Nose, Throat and Bronchi. John R. Richardson: instructor in laryngology, Harvard Medical School; assistant surgeon, Massachusetts Eye and Ear Infirmary; assistant surgeon, Massachusetts General Hospital.

APRIL 22. DISEASES OF THE CHEST. *Chairmen*: Donald S. King and John W. Strieder.

5:00–5:30. Public-Health Aspects of Tuberculosis in Massachusetts. Alton S. Pope: deputy commissioner and director of the Division of Tuberculosis, Massachusetts Department of Public Health.

5:30–6:00. The Present Concept of the Treatment of Pulmonary Tuberculosis. Paul Dufault: superintendent, Rutland State Sanatorium.

6:00–6:30. Important Points to Remember in Treating Lung Conditions. Theodore L. Badger: chief-of-staff, Channing Home; instructor in medicine, Harvard Medical School.

7:30–8:15. Pulmonary Carcinoma and Other Growths in the Chest. Ralph H. Adams: surgeon, Lahey Clinic.

8:15–9:00. Pulmonary Abscess, Bronchiectasis and Other Suppurative Chest Conditions. Richard H. Sweet: associate visiting surgeon, Massachusetts General Hospital; instructor in surgery, Harvard Medical School.

APRIL 24. NEUROPSYCHIATRY. *Chairmen*: Raymond D. Adams and Harry C. Solomon.

3:00–3:35. Psychosomatic Medicine. Stanley Cobb: psychiatrist-in-chief, Massachusetts General Hospital.

3:35–4:05. Psychoneurosis and the Veteran. John Murray: consultant in psychiatry, Massachusetts Institute of Technology.

4:05–4:40. Insulin-Shock and Electric-Shock Therapy and Lobotomy. Gaylord P. Coon: medical officer, Boston Psychopathic Hospital; junior associate, Peter Bent Brigham Hospital.

4:40–5:20. Neurosyphilis. Augustus S. Rose: member of staff, Psychopathic Hospital; consultant, Massachusetts General, Peter Bent Brigham, New England Baptist and Newton hospitals.

5:20–6:00. Epilepsy. William G. Lennox: visiting physician, Children's Hospital; visiting neurologist, Boston City Hospital; assistant in neurology, Peter Bent Brigham Hospital.

APRIL 29. NEUROPSYCHIATRY (*Continued*).

5:00–5:30. Headache. Derek Denny-Brown: professor of neurology, Harvard Medical School; director, Neurological Unit, Boston City Hospital.

5:30–6:00. Pyogenic Intracranial Infections. Charles S. Kubik: neurologist and neuropathologist, Massachusetts General Hospital.

6:00–6:30. Apoplexy. Raymond D. Adams: visiting neurologist and neuropathologist and assistant director, Neurological Unit, Boston City Hospital; consultant in neurology, Pratt Diagnostic Hospital; lecturer in neurology, Tufts College Medical School.

APRIL 29. ENDOCRINOLOGY. *Chairmen*: Edwin B. Astwood and Lewis M. Hurxthal.

7:30–8:15. Progress in Endocrinology and Thiouracil in the Treatment of Hyperthyroidism. Edwin B. Astwood: research professor of medicine, Tufts College Medical School.

8:15–9:00. Diagnosis and Treatment of Thyroid Disease. Frank H. Lahey: director, Lahey Clinic; surgeon-in-chief, New England Baptist and Deaconess hospitals.

MAY 1. ENDOCRINOLOGY. *Chairmen*: Edwin B. Astwood and Lewis M. Hurxthal.

3:00–3:30. Childhood Obesity and Related Problems. Richard Wagner: assistant professor of pediatrics, Tufts College Medical School; physician, Boston Floating Hospital.

3:30–4:00. Hypothyroidism and Hypopituitarism. Lewis M. Hurxthal: director, Department of Medicine, Lahey Clinic; physician, New England Baptist and Deaconess hospitals.

4:00–4:30. Treatment of Addison's Disease. George W. Thorn: Hersey Professor of the Theory and Practice of Physic, Harvard Medical School; physician-in-chief, Peter Bent Brigham Hospital.

4:30–5:15. Hyperparathyroidism. Oliver Cope: assistant professor of surgery, Harvard Medical School; associate visiting surgeon, Massachusetts General Hospital.

5:15–6:00. Male Hypogonadism and the Therapeutic Use of Androgens. Robert W. Williams: associate in medicine, Harvard Medical School; junior visiting physician and assistant, Thorndike Memorial Hospital, Boston City Hospital.

MAY 6. DISEASES OF THE EYE. *Chairmen*: Edwin B. Dunphy and Benjamin Sachs.

5:00–6:00. Ophthalmology in General Practice. Benjamin Sachs: professor of ophthalmology, Tufts College Medical School. Edwin B. Dunphy: chief of ophthalmology, Massachusetts Eye and Ear Infirmary.

DIABETES MELLITUS. *Chairmen*: W. Richard Ohler and Howard F. Root.

6:00–6:30. Diagnostic Methods. Priscilla White: instructor in pediatrics, Tufts College Medical School; physician, New England Deaconess Hospital.

Dietary Treatment. Joseph Rosenthal: assistant professor of medicine, Tufts College Medical School; supervisor in charge of teaching, Boston Dispensary.

7:30–9:00

The Insulins. George Ballantyne: director, Diabetic Clinic, Worcester City Hospital.

Complications. James Townsend: associate physician, Massachusetts General Hospital.

Acidosis and Coma. Howard F. Root: associate in medicine, Harvard Medical School; physician-in-chief, New England Deaconess Hospital.

Advances in Diabetes. Elliott P. Joslin: clinical professor of medicine (emeritus), Harvard Medical School; medical director, George F. Baker Clinic, New England Deaconess Hospital.

MAY 8. GYNECOLOGY. *Chairmen*: Joe V. Meigs and John Rock.

3:00–3:45. Menstruation, Its Disorders and Their Treatment. John Rock: instructor in gynecology, Harvard Medical School; visiting surgeon, Free Hospital for Women.

3:45–4:30. Office Problems, Diagnostic Methods and Treatment. James C. Janney: professor of gynecology, Boston University School of Medicine.

4:30–5:15. Diagnosis of Cancer. Joe V. Meigs: clinical professor of gynecology, Harvard Medical School; chief, Vincent Memorial Hospital and Gynecological Service, Massachusetts General Hospital.

5:15–6:00. Treatment of Cancer. George Van S. Smith: visiting surgeon and director of the Fearing Research Laboratory, Free Hospital for Women.

MAY 13. OBSTETRICS. *Chairmen*: Alonzo K. Paine and Duncan E. Reid.

5:00–6:30 and *7:30–9:00.* A Critical Review of Progress in Obstetrics During the Last Four Years, including a Consideration of Certain Immediate Problems of the Newborn. Roy J. Heffernan: visiting obstetrician and gynecologist, Carney Hospital. Harold H. Rosenfield: visiting surgeon in obstetrics and gynecology, Boston City Hospital. Stewart H. Clifford: pediatrician, Boston Lying-in Hospital; associate visiting physician, Children's Hospital. Arthur T. Hertig: pathologist and obstetrician to Out-Patient Department, Boston Lying-in Hospital.

MAY 15. SURGICAL GENITOURINARY DISEASES AND VENEREAL DISEASES. *Chairmen*: Roger C. Graves and Samuel N. Vose.

3:00–3:40. Prostatism. George G. Smith: visiting urologist, Massachusetts General Hospital; urologist, Palmer Memorial Hospital.

3:40–4:25. The Female Bladder. Samuel N. Vose: professor of genitourinary surgery, Boston University School of Medicine; urologist, Massachusetts Memorial Hospitals.

4:25–5:00. Epidemiology of Venereal Disease. Erwin C. Dresher: surgeon, United States Public Health Service.

5:00–5:30. Recent Advances in the Management of Gonorrhea in the Male. J. Hartwell Harrison: urological surgeon, Peter Bent Brigham Hospital.

5:30–6:00. Progress in the Diagnosis and Treatment of Syphilis. John G. Downing: professor of dermatology and syphilology, Tufts College Medical School; professor of dermatology, Boston University School of Medicine; dermatologist-in-chief, Massachusetts Memorial, Boston City and St. Elizabeth's hospitals.

CORRESPONDENCE

DEPRIVATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held March 15, the Board took the following actions:

To suspend the registration of Dr. Edmond J. MacDonald, 24 Wheatland Street, Somerville, for six months because of gross misconduct in the practice of his profession as shown by his treatment of patients.

To revoke the registration of Dr. Earl Burton Carr of Cassadago, New York, and Bar Harbor, Maine, because of gross misconduct in the practice of his profession as shown by his conviction of a felony in New York State.

H. QUIMBY GALLUPE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

(*Notices on page xix*)